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Datasheet for the decision of 16 November 2009

Case Number: W 0009/09 - 3.3.04

Application Number: PCT/US 2007/023387

Publication Number: WO 2008/143639

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:
Gene expression profiling for identification, monitoring and treatment of cervical cancer

Applicant:
Source Precision Medicine, Inc. et al.

Opponent:
-

Headword:
Gene expression profiling V/SOURCE PRECISION MEDICINE

Relevant legal provisions:
PCT Art. 17(3)(a)
PCT R. 13.1, 13.2, 13.3, 40.1, 40.2(c)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Lack of unity a posteriori (yes)"

Decisions cited:
G 0001/89, W 0006/90, W 0016/08

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: W 0009/09 - 3.3.04

International Application No. PCT/US 2007/023387

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 16 November 2009

Applicant:
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Decision under appeal:
Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 11 February 2009.

Composition of the Board:

Chairman: U. Kinkeldey
Members: B. Claes
T. Bokor

Summary of Facts and Submissions

I. International patent application no. PCT/US2007/023387 published as WO 2008/143639 and having the title "Gene expression profiling for identification, monitoring and treatment of cervical cancer" was filed on 6 November 2007 with 23 claims.

II. Independent claims 1 to 4 and 24 read as follows:

"1. A method for evaluating the presence of cervical cancer in a subject based on a sample from the subject, the sample providing a source of RNAs, comprising:

a) determining a quantitative measure of the amount of at least one constituent of any constituent of any one table selected from the group consisting of Tables 1, 2, 3, 4, and 5 as a distinct RNA constituent in the subject sample, wherein such measure is obtained under measurement conditions that are substantially repeatable and the constituent is selected so that measurement of the constituent distinguishes between a normal subject and a cervical cancer- diagnosed subject in a reference population with at least 75% accuracy; and

b) comparing the quantitative measure of the constituent in the subject sample to a reference value.

2. A method for assessing or monitoring the response to therapy in a subject having cervical cancer based on a sample from the subject, the sample providing a source of RNAs, comprising:

a) determining a quantitative measure of the amount of at least one constituent of any constituent of Tables 1, 2, 3, 4, and 5 as a distinct RNA

constituent, wherein such measure is obtained under measurement conditions that are substantially repeatable to produce subject data set; and

b) comparing the subject data set to a baseline data set.

3. A method for monitoring the progression of cervical cancer in a subject, based on a sample from the subject, the sample providing a source of RNAs, comprising:

a) determining a quantitative measure of the amount of at least one constituent of any constituent of Tables 1, 2, 3, 4, and 5 as a distinct RNA constituent in a sample obtained at a first period of time, wherein such measure is obtained under measurement conditions that are substantially repeatable to produce a first subject data set;

b) determining a quantitative measure of the amount of at least one constituent of any constituent of Tables 1, 2, 3, 4, and 5 as a distinct RNA constituent in a sample obtained at a second period of time, wherein such measure is obtained under measurement conditions that are substantially repeatable to produce a second subject data set; and

c) comparing the first subject data set and the second subject data set.

4. A method for determining a cervical cancer profile based on a sample from a subject known to have cervical cancer, the sample providing a source of RNAs, the method comprising:

a) using amplification for measuring the amount of RNA in a panel of constituents including at least 1 constituent from Tables 1, 2, 3, 4, and 5 and

b) arriving at a measure of each constituent, wherein the profile data set comprises the measure of each constituent of the panel and wherein amplification is performed under measurement conditions that are substantially repeatable.

23. A kit for detecting cervical cancer in a subject, comprising at least one reagent for the detection or quantification of any constituent measured according to any one of claims 1-22 and instructions for using the kit."

Dependent claims 5 to 22 define further embodiments of the methods in accordance with the preceding claims.

Tables 1 to 5 referred to in the claims are labelled as a so-called "Profile" and list numerous genes of various origin. The lists in the tables partially overlap. Table 1 is labelled "Precision Profile™ for Cervical Cancer" and lists 78 genes by their gene symbol (the first gene appearing in table 1 e.g. being ALOX12), their gene name (for ALOX12 e.g.: "arachidonate 12-lipoxygenase") and their gene accession number (for ALOX12 e.g.: NM_000697). Table 1 also lists the gene BRAF.

III. On 11 February 2009, the European Patent Office (EPO), acting in its capacity as International Searching Authority (ISA) under Article 16 PCT and Article 154 EPC informed the applicant in an invitation under Article 17(3)(a) PCT and Rule 40.1) PCT that the application did not comply with the requirement of unity of invention (Rule 13.1 PCT) and invited the

applicant to pay within a time limit of one month two-hundred and eighty nine (289) additional search fees.

IV. In the invitation to pay additional fees, the ISA defined the two-hundred and ninety (290) inventions to which the application related as follows:

"1. claims: 1–23 (partially)

INVENTION 1:

Method for a) evaluating the presence of cervical cancer in a subject, b) assessing or monitoring the response to therapy of cervical cancer, c) monitoring the progression of cervical cancer in a subject, and d) determining a cervical cancer profile based on a sample from a s [*sic*] subject, as well as a kit for detecting cervical cancer in a subject, making use of the marker gene ALOX12.

2. claims: 1–23 (partially)

INVENTIONS 2–290:

Method for a) evaluating the presence of cervical cancer in a subject, b) assessing or monitoring the response to therapy of cervical cancer, c) monitoring the progression of cervical cancer in a subject, and d) determining a cervical cancer profile based on a sample from a s subject, as well as a kit for detecting cervical cancer in a subject, making use of the marker genes listed in tables 1–5, beginning with ANGPT1 (Tab.1; INVENTION 2), and ending with ZNF35O (Tab.5; INVENTION 290)."

V. The ISA referred in the invitation to the following documents:

(1) Wong *et al*. (2006), Int. J. Cancer, Vol. 118, pages 2461-2469.

(2) Santin *et al*. (2005), Virology, Volume 331, pages 269-291.

(3) Bachtiary *et al*. (2006), Clin. Cancer Res., Vol. 12, No. 19, pages 5632-5640.

(4) US2006/0154275

VI. The reasons for the finding of non-unity by the ISA was that the common concept of the application, which was the use of "constituents" (i.e. marker genes) that are differentially expressed in methods for a) evaluating the presence of cervical cancer, b) assessing or monitoring the response to therapy of cervical cancer, c) monitoring the progression of cervical cancer, d) determining a cervical cancer profile, as well as a kit for detecting cervical cancer in a subject involving comparison of quantification of the marker genes to reference values, was known from the state of the art represented by *inter alia* each of documents (1) to (4).

The problem to be solved by the application was considered the need to identify further gene markers for cervical cancer, suitable within the methods and the kit as formulated in the common concept. The solution was the use of each of the cervical cancer marker genes listed in tables 1–5 which each constituted an individual alternative solution to the

problem as defined which were not linked. Hence, the ISA considered that the application contained two-hundred and ninety inventions as identified above.

VII. The communication dated 11 February 2009 also contained the results of the partial international search which was established for the invention first mentioned in the claims, i.e. invention 1 relating to the marker gene ALOX12.

VIII. With a letter dated 11 March 2009, the applicants paid one additional search fee under protest. If the ISA required that the invention be restricted to one gene only for search purposes only than the applicants requested the additional search to be conducted with respect to the BRAF gene.

The applicants argued that the ISA had failed to search the invention as defined in the claims and specification and that the restriction of the primary invention to a single gene was improper.

The methods of the invention used statistical methods (e.g. stepwise logistic regression analysis) to analyse the expression levels of genes that had been implicated in cervical cancer in a sample isolated from a subject. To evaluate genes capable of discriminating between healthy subjects and subjects suffering from cervical cancer, the genes were first evaluated and then statistically ranked according to their significance value. Stepwise logistic regression analysis was then used to evaluate the significance of the remaining ranked genes to identify a second gene, which in combination with the first and most significant gene

identified, improved the ability of the one-gene model to discriminate between the two subject groups. Additional rounds of logistic regression analysis might be performed to identify a third gene which further improved the ability of the two-gene model to distinguish between the two subject groups, etc. While an infinite number of combinations of genes shown in tables 1-5 could be identified, capable of distinguishing between the two subject populations, a cut off of 75% classification accuracy was imposed for selecting gene-models capable of distinguishing between the two subject groups.

In tables 1A-5A of the application as published, all of the possible one-, two- and/or three-gene combinations (i.e. gene models) for the genes shown in tables 1-5, capable of distinguishing between healthy, normal subjects and cervical cancer subjects with at least 75% classification accuracy using the claimed methods, had been identified and enumerated. This exhaustive disclosure of gene models identified using the methods justified a search if the claims with respect to all the genes listed in tables 1-5.

The applicants requested the reimbursement of the additional search fee and that the ISA withdrew the objection for lack of unity and searches the invention as claimed with respect of all the genes in tables 1-5.

IX. On 8 April 2009, the ISA invited the applicants to pay a protest fee and informed the applicant that a prior review of the justification for the invitation to pay additional fees had confirmed that the invitation to pay such fees was justified.

X. With letter of 8 May 2009 the applicants authorised the ISA to charge its deposit account for the payment of the protest fee.

Reasons for the Decision

Competence and admissibility

1. Given that the application was filed on 6 November 2007, the protest is subject to the provisions of the PCT as in force from 1 April 2007. The boards of appeal are responsible for deciding on protests relating to PCT applications pending at the time of entry of the EPC 2000. Details of the procedure are guided by the Decision of the President of the EPO dated 24 June 2007, Article 3 (OJ EPO 2007, Special Edition No.3, 140), see also W 16/08, points 1.1 to 1.5 of the reasons.

2. The invitation under Article 17(3)(a) PCT to pay additional fees is reasoned in accordance with Rule 40.1 PCT.

3. The protest against the invitation by the ISA to pay additional fees was filed in time, is reasoned and is hence admissible.

Substantive matters

4. According to Rule 13.1 PCT, the international patent application shall relate to one invention only or to a group of inventions so linked as to form a single inventive concept. If the ISA considers that the claims

lack unity of invention, it is empowered, under Article 17(3)(a) PCT, to invite the applicant to pay additional fees.

5. According to Rule 13.2 PCT, where a group of inventions is claimed in one and the same application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features, whereby the expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

6. According to Rule 13.3 PCT the determination of whether a group of inventions is so linked as to form a single inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

7. Lack of unity may be directly evident *a priori*, i.e. before the examination of the merits of the claims in comparison with the state of the art revealed by the search (see for example, decision W 6/90, OJ EPO 1991, 436). Alternatively, having regard to decision G 1/89 of the Enlarged Board of Appeal (OJ EPO 1991, 155), the ISA may also raise an objection *a posteriori*, i.e. after having taken the prior art revealed by the search into closer consideration. This practice is laid down in the PCT International Search Guidelines (Chapter 10, pages 75 to 100) which are the basis for a uniform practice of all international search authorities. In its decision, the Enlarged Board of Appeal indicated

that such consideration represents only a provisional opinion on novelty and inventive step which is in no way binding upon the authorities subsequently responsible for the substantive examination of the application (point 8.1 of the Reasons for the decision). In point 8.2 of the Reasons, the Enlarged Board mentioned that such invitation to pay additional fees should always be made "with a view to giving the applicant fair treatment" and should only be made in clear cases.

8. The question to be decided by the board here is whether the subject-matter of those inventions for which search fees have been paid by the applicant, namely the invention identified by the ISA relating to gene ALOX12 and the invention identified by the ISA and elected by the applicant relating to the BRAF gene (see Sections IV and VIII above), are so linked as to form a single inventive concept or not.

9. The invention identified by the ISA relating to gene ALOX12 and the invention identified by the ISA and elected by the applicant relating to the BRAF gene as defined in the independent claims 1 (method for evaluating the presence of cervical cancer in a subject), 2 (method for assessing or monitoring the response to therapy in a subject having cervical cancer), 3 (method for monitoring the progression of cervical cancer in a subject), 4 (method for determining a cervical cancer profile based on a sample from a subject known to have cervical cancer) and 23 (kit for detecting cervical cancer in a subject) relate to the use of "constituents" or marker genes that are differentially expressed in healthy subjects and in

subjects suffering from cervical cancer. This is in agreement with the opinion of the ISA (see section VI above). Confirmation for this finding can be found in the description of the application as filed on page 1, lines 8 to 11, where it is stated that: "[t]*he present invention relates generally to the identification of biological markers associated with the identification of cervical cancer. More specifically, the present invention relates to the use of gene expression data in the identification, monitoring and treatment of cervical cancer and the characterization and evaluation of conditions induced by or related to cervical cancer.*"

10. The board agrees with the ISA's finding in the invitation to pay additional fees that the use of "constituents" or marker genes that are differentially expressed in healthy subjects and in subjects suffering from cervical cancer was known in the state of the art.

Indeed, document (1) discloses genome-wide gene expression profiling of cervical cancer based on oligonucleotide microarray analysis, real—time quantitative RT-PCR and data reference validation. It specifically highlights the correlation of the expression of *inter alia* CDKN2A, VEGF and ALOX12, with cervical cancer (see table II).

Document (2) discloses numerous of the cervical cancer marker genes of the present invention established by microarray analysis and q-RT—PCR data validation and gene expression profiles of primary HPV16- and HPV18-infected early stage cervical cancers and normal cervical epithelium which are suitable for cervical

cancer diagnosis, prognosis and therapy. Document (2) discloses *inter alia* CDKN2A, PTGES, TOP2A, UBE2C, CD97, E2F1, TGFB1, CFLAR, SERPING1 and TFPI2 as suitable markers.

Document (3) discloses gene expression profiling in cervical cancer, based on microarray analysis, normalization of data, and QRT—PCR. Highlighted are *inter alia* genes 1L8 and VEGF as suitable marker genes.

Document (4) discloses methods for the diagnosis or staging of cervical cancer based on quantitative gene expression regulation of marker genes listed in the patent in the tables, including *inter alia* the MYBL2 gene.

11. In view of this prior art, the technical problem underlying the two searched inventions was the provision of alternatives to the known "constituents" or marker genes that are differentially expressed in healthy subjects and in subjects suffering from cervical cancer. As solutions to this problem the first searched invention provides the ALOX12 gene and the second searched invention provides the BRAF gene.

12. The board cannot recognise structural characteristics or effects common to the two genes provided according to the searched group of inventions common to all claims which go beyond that they are differentially expressed in healthy subjects and in subjects suffering from cervical cancer and could hence represent "special technical features" within the meaning of Rules 13.2 and 13.3 PCT. Therefore the board must conclude that the solutions to the above technical problem as

provided by the two searched inventions do not share a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT *a posteriori*.

13. The above analysis of prior art cited in the partial search report provided by the ISA, thus establishes that the technical relationship as defined above between the two searched inventions does not involve "special technical features" and can therefore not provide unity of invention in accordance with Rule 13.2 PCT.

14. The applicants have argued that the ISA had failed to search the invention as defined in the claims and specification and that the restriction of the primary invention to a single gene was improper.

15. The board notes however, that, as can be taken from the wording of independent claims 1 to 4, the claimed methods concern "determining a quantitative measure of the amount of at least one constituent of any constituent (of any one table selected from the group consisting) of Tables 1, 2, 3, 4, and 5 as a distinct RNA constituent" (claim 1) or similarly "determining a quantitative measure of the amount of at least one constituent of any constituent of Tables 1, 2, 3, 4, and 5 as a distinct RNA constituent" or similarly "at least 1 constituent from Tables 1, 2, 3, 4, and 5 (claims 2 to 4) (emphasis added by the board). The kit of claim 23 is stated to be "comprising at least one reagent for the detection or quantification of any constituent measured according to any one of claims 1 to 22". The board therefore also concurs with the ISA

that both the identified invention relating to gene ALOX12 and the invention defined by the applicant with respect to the BRAF gene (see Sections IV and VIII above) are subject-matter of the claimed invention.

16. In addition the board notes that the wording of the claims do not mention statistical methods (e.g. stepwise logistic regression analysis) to analyse the expression levels of genes that had been implicated in cervical cancer in a sample isolated from a subject. Nor do they commonly refer to a cut off of 75% classification accuracy for selecting gene models capable of distinguishing between the two subject groups or gene models disclosed in tables 1A-5A of the application as published which recites all of the possible one-, two- and/or three-gene combinations (i.e. gene models) for the genes shown in tables 1 to 5, capable of distinguishing between healthy, normal subjects and cervical cancer subjects with at least 75% classification accuracy using the claimed methods. Only for this reason therefore the further arguments of the applicants that the search should not have been restricted to one gene must fail.

17. As a consequence of the above considerations the two groups of inventions searched by the ISA are not so linked as to form a single inventive concept. Consequently, the application is considered not to comply with the requirements of unity of invention under Rule 13.1 PCT, and the invitation to pay additional fees with respect to the invention identified in relation to the BRAF gene was justified.

Order

For these reasons it is decided that:

The protest under Rule 40.2(c) PCT is dismissed.

The Registrar | The Chair

C. Eickhoff | U. Kinkeldey