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**Datasheet for the decision
of 1 July 2009**

Case Number: W 0004/09 - 3.3.04

Application Number: PCT/US2007/023425

Publication Number: WO 2008/121132

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:

Gene expression profiling for identification, monitoring and
healment of prostate cancer

Applicant:

Source Precision Medicine, Inc.

Headword:

Gene expression profiling IV/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):

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Keyword:

"Lack of unity a posteriori (yes)"

Decisions cited:

G 0001/89, W 0006/90, W 0016/08

Catchword:

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Case Number: W 0004/09 - 3.3.04

International Application No. PCT/US2007/023425

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 1 July 2009

Appellant: Source Precision Medicine, Inc.
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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
14 October 2008.

Composition of the Board:

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

Summary of Facts and Submissions

I. International patent application no. PCT/US2007/023425 published as WO 2008/121132 and having the title "Gene expression profiling for identification, monitoring and treatment of prostate cancer" was filed on 6 November 2007 with 23 claims.

II. Independent claims 1 to 4 and 23 read as follows:

"1. A method for evaluating the presence of prostate 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, and 4 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 prostate 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 prostate 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, and 4 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 prostate 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, and 4 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, and 4 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 prostate cancer profile based on a sample from a subject known to have prostate 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, and 4 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 prostate 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 4, referred to in the claims each list numerous genes of various origin by their gene symbol (the first gene appearing in table 1 e.g. being ABCC1), their gene name (for ABCC1 e.g.: "ATP-binding cassette, sub-family C (CFTR/MRP), member 1") and their gene accession number (for ACSL5 e.g.: NM_004996). The list in the tables partially overlap. Each table is labelled as a so-called "Profile". Table 1 is labelled "Precision ProfileTM for Prostate Cancer" and lists 74 genes, including the CDH1 gene.

III. On 14 October 2008, 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 ninety (290) additional search fees.

IV. In the invitation to pay additional fees, the ISA defined the two-hundred and ninety one (291) inventions to which the application related as follows:

"1. claims: 1-23 (partially)

INVENTION 1:

Method for a) evaluating the presence of prostate cancer in a subject, b) assessing or monitoring the response to therapy of prostate cancer in a subject, c) monitoring the progression of prostate cancer in a subject, and d) determining a prostate cancer profile base on a sample from a subject, as well as a kit for detecting prostate cancer in a subject, making use of the marker gene ABCC1.

2. claims: 1-23 (partially)

INVENTIONS 2-291:

Method for a) evaluating the presence of prostate cancer in a subject, b) assessing or monitoring the response to therapy of prostate cancer in a subject, c) monitoring the progression of prostate cancer in a subject, and d) determining a prostate cancer. profile base on a sample from a subject, as well as a kit for detecting prostate cancer in a subject, making use of the marker genes as listed in tables 1-4, beginning with ACP (Tab.1; invention 2), and ending with WT1 (Tab.4; invention 291)."

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

- (1) WO 2003/012067
- (2) Lapointe *et al.* (2004), PNAS, Vol. 101, pages 811-816.
- (3) Glinsky *et al.* (2004), J. Clin. Investigation, Vol. 113, pages 913-923.
- (4) Schummer *et al.* (1999), Urol. Res., Vol. 27, pages 164-168.
- (5) Latil *et al.* (2003), Clin. Cancer Res., Vol. 9, pages 5477-5485.
- (6) Kristiansen *et al.* (2005), J. Pathol., Vol. 205, pages 359-376.

VI. The ISA defined the common concept of the application as the use of "constituents" (= marker genes) being differentially expressed, and making use of the latter in methods for a) evaluating the presence of prostate cancer, b) assessing or monitoring the response to therapy of prostate cancer, c) monitoring the progression of prostate cancer, d) determining a prostate cancer profile base, and using them in a kit for detecting prostate cancer in a subject. The common concept of the methods of the application further referred to comparing quantification of the marker genes to reference values. This common concept was however known from the state of the art represented by

documents (1) to (6) so that no unity of invention was given.

In view of this prior art, the problem to be solved by the application was considered as the need to identify further gene markers for prostate cancer, suitable within the methods and the kit as formulated in the common concept. The solution of the application was reflected in the enlisted genes of tables 1-4, which did not comprise any additional technical, structural or functional feature which would render it possible to "group" them together in one single concept or further (sub-)concepts. The ISA considers the use of each individual marker of the tables 1-4 as an individual alternative solution to the problem as defined and consequently the application contained two-hundred and ninety one inventions as identified above.

VII. The communication dated 14 October 2008 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 ABCC1.

VIII. With a letter dated 14 November 2008, the applicant 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 applicant requested the additional search to be conducted with respect to the gene CDH1.

The applicant argued that the ISA had failed to search the invention as defined in the claims and the

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 prostate cancer in a sample isolated from a subject. To evaluate genes capable of discriminating between healthy subjects and subjects suffering from prostate 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 1-4 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-4A of the application as filed, all of the possible one- and two-gene combinations (i.e. gene models) for the genes shown in tables 1-4, capable of distinguishing between healthy, normal subjects and ovarian 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 of the invention justified a search of the claims with respect to all the genes listed in tables 1-4.

The applicants requested the reimbursement of the additional search fee and that the ISA withdraws the objection for lack of unity and searches the invention as claimed with respect of all the genes in tables 1-4.

- IX. On 16 January 2009, the ISA invited the applicant 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 2 February 2009 the applicant 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 ABCC1 and the invention identified by the ISA and elected by the applicant relating to the CDH1 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 ABCC1 and the invention identified by the ISA and elected by the applicant relating to the CDH1 gene as defined in the independent claims 1 (method for evaluating the presence of prostate cancer in a subject), 2 (method for assessing or monitoring the response to therapy in a subject having prostate cancer), 3 (method for monitoring the progression of prostate cancer in a subject), 4 (method for determining a prostate cancer profile based on a sample from a subject known to have prostate cancer) and 23 (kit for detecting prostate 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 prostate cancer. This corresponds 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 12, where it is stated that: "*[t]he present invention relates generally to the identification of biological markers associated with the identification of prostate cancer. More specifically, the present invention relates to the use of gene expression data in the identification, monitoring and treatment of prostate cancer and the characterization and evaluation of conditions induced by or related to prostate cancer.*"

The board agrees to 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 prostate cancer was known in the state of the art.

Indeed, document (1) discloses methods and compositions for gene expression profiling of prostate cancer marker genes based on quantitative RT-PCR, suitable for assessment of the presence of prostate cancer, as well as prognosis, progression and recurrence following therapy (see e.g. page 3 lines 5 to 9). The document particularly discloses e.g. ADAMTS1, EGR1, IGFBP3, JUN, MCAM and NRAS as marker genes, suitable for such expression profiling (see e.g. page 6, lines 23 to 25).

Similarly, document (2) discloses expression profiling of ca. 26.000 genes (amongst them Mucl), allowing subtyping of prostate cancer, progression prognosis and recurrence prediction (see abstract). Also document (3) discloses expression profiling of 12.625 genes, including FOS (table 1), allowing the prediction or recurrence of prostate cancer with 90% and 75% accuracy, based on a so-called "gene expression-based recurrence predictor algorithm" (see abstract and last paragraph of the "discussion", tables 1 to 3).

Document (5) discloses profiling of prostate cancer gene expression (291 genes) by quantitative real-time RT-PCR and reveals 46 genes which are differentially expressed in prostate cancer, and four which are especially suitable for assessment of progression and recurrency (see abstract, figure 1). Similarly, document (6) discloses gene expression profiling and the identification of 277 genes which are differentially expressed between prostate cancer and normal tissue, as measured by quantitative RT-PCR. This

- allowed prognosis and recurrence prediction (see abstract, page 361, right-hand column lines 8 and tables 2 and 3).
10. 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 prostate cancer. As solutions to this problem the first searched invention provides the ABCC1 gene and the second searched invention provides the CDH1 gene.
 11. 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 prostate 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*.
 12. 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.

13. The applicant has 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.

14. 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, and 4 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, and 4 as a distinct RNA constituent" or similarly "at least 1 constituent from Tables 1, 2, 3, and 4 (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 ABCC1 and the invention defined by the applicant with respect to the CDH1 gene (see Sections IV and VIII above) are subject-matter of the claimed invention.

15. In addition the board notes that the wordings 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 ovarian cancer in a sample isolated from a subject. Nor do the claims 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-4A of the application as published which recites all of the possible one- and two-gene combinations (i.e. gene models) for the genes shown in tables 1 to 4, capable of distinguishing between healthy, normal subjects and prostate 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.

16. 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 DLC1 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

P. Cremona

U. Kinkeldey