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**Datasheet for the decision
of 27 April 2009**

Case Number: W 0041/08 - 3.3.04

Application Number: PCT/US 2007/023386

Publication Number: WO 2008/069881

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:

Gene expression profiling for identification, monitoring and treatment of melanoma

Applicant:

Source Precision Medicine, Inc. et al

Opponent:

-

Headword:

Gene expression profiling I/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 0041/08 - 3.3.04

International Application No. PCT/US 2007/023386

D E C I S I O N
of the Technical Board of Appeal
of 27 April 2009

Applicant: Source Precision Medicine, Inc. et al.
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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
26 September 2008 .

Composition of the Board:

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

Summary of Facts and Submissions

I. International patent application no. PCT/US2007/023386 published as WO 2008/069881 and having the title "Gene expression profiling for identification, monitoring and treatment of melanoma" was filed on 6 November 2007 with 24 claims.

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

"1. A method for evaluating the presence of melanoma 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, 5 and 6 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 melanoma-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 melanoma 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, 5, and 6 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 melanoma 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, 5, and 6 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, 5, and 6 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 melanoma profile based on a sample from a subject known to have melanoma, 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, 5, and 6 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.

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

Dependent claims 5 to 23 define further embodiments of the methods in accordance with the preceding claims.

Tables 1 to 6, 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 AKT1), their gene name (for AKT 1 e.g.: "v-akt murine thymoma viral oncogene homolog 1") and their gene accession number (for AKT1 e.g.: NM_005163). The list in the tables partially overlap. Each table is labelled as a so-called "Profile". Table 1 is labelled "Precision ProfileTM for Melanoma" and lists 63 genes. Table 2 is labelled "Precision ProfileTM for Inflammatory Response" and lists 75 genes, including MYC.

III. On 26 September 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 four-hundred and forty seven (447) additional search fees.

IV. In the invitation to pay additional fees, the ISA defined the four-hundred and forty eight (448) inventions to which the application related as follows:

1. claims 1-24 (partially)

Invention Number 1:

Methods for (1.) evaluating the presence of melanoma / (2.) assessing or monitoring the response to therapy / (3.) monitoring the progression of melanoma / (4.) determining a melanoma profile, as well as a kit for detecting melanoma cancer in a subject, making use of the marker gene AKT1.

2. claims 1-24 (partially)

Inventions 2 - 448:

Methods for (1.) evaluating the presence of melanoma / (2.) assessing or monitoring the response to therapy / (3.) monitoring the progression of melanoma / (4.) determining a melanoma profile, as well as a kit for detecting melanoma cancer in a subject, making use of the marker genes as listed in tables 1 - 6, beginning with APAF1 (second line table 1) and ending with ZDHHC2.

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

(1) WO 04/045521

- (2) Kuo *et al.* (1998), *Clinical Cancer Research*, Vol. 4, pages 411-418.
- (3) Bitisik *et al.* (2003), *J. Biochemistry and Molecular Biology*, Vol. 36, No. 2, pages 173-178.
- (4) Juergensen *et al.* (2001), *Tumor Biology*, Vol. 22., pages 54-58.

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" or marker genes that are differentially expressed in methods for (1.) evaluating the presence of melanoma / (2.) assessing or monitoring the response to therapy / (3.) monitoring the progression of melanoma / (4.) determining a melanoma profile, as well as a kit for detecting melanoma cancer in a subject, was known from the state of the art represented by e.g. each of documents (1) to (4).

The problem to be solved by the application was considered to be the finding of yet further melanoma cancer markers to be used in methods for (1.) evaluating the presence of melanoma / (2.) assessing or monitoring the response to therapy / (3.) monitoring the progression of melanoma / (4.) determining a melanoma profile, as well as a kit for detecting melanoma cancer in a subject. The solution was the use of the melanoma markers as listed in tables 1 to 6. The ISA considered the use of each of the melanoma markers of tables 1 to 6 an individual solution to the problem to be solved. Hence, the ISA considered that the application contained four-hundred and eight inventions as identified above.

VII. The communication dated 26 September 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 AKT1.

VIII. With a letter dated 23 October 2008, 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 MYC 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 melanoma in a sample isolated from a subject. To evaluate genes capable of discriminating between healthy subjects and subjects suffering from melanoma, 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 1-6 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-6A 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 1-6, capable of distinguishing between healthy, normal subjects and melanoma 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 1-6.

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 1-6.

- IX. On 21 November 2008, 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 December 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 AKT1 and the invention identified by the ISA and elected by the applicant relating to the MYC 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 AKT1 and the invention identified by the ISA and elected by the applicant relating to the MYC gene as defined in the independent claims 1 (method for evaluating the presence of melanoma in a subject), 2 (method for assessing or monitoring the response to therapy in a subject having melanoma), 3 (method for monitoring the progression of melanoma in a subject), 4 (method for determining a melanoma profile based on a sample from a subject known to have melanoma) and 24 (kit for detecting melanoma 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 melanoma. 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 skin cancer. More specifically, the present invention relates to the use of gene expression data in the identification, monitoring and treatment of skin cancer and the characterization and evaluation of conditions induced by or related to skin cancer."

10. 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 melanoma was known in the state of the art.

Indeed, document (1) discloses *inter alia* a method of detecting melanoma cells in a patient comprising quantitative real time RT-PCR assay for detecting the presence or absence of nucleic acid targets indicative for metastatic melanoma. Claim 1 defines such a method using a panel comprising GalNAcT (1-4-N-Acetylgalactosaminyl-transferase), transcription factor PAX3, or both. The panel might further comprise markers selected from a group consisting of MAGE-A3, GalNAcT, Mart-1, PAX3, MITF, TRP-2, and tyrosinase (e.g. claim 3).

Document (2) also identifies GalNAcT as a molecular marker for "detecting, characterising and monitoring the progression of" metastatic melanoma.

Document (3) discloses the detection of circulating melanoma cells by a two marker PCR assay in relation to therapy. The document identifies the marker genes tyrosinase and Melan A as predictive for therapeutic

response in a clinical setting and for monitoring the efficacy of the treatment (page 176, left-hand column, lines and right-hand column, lines 31 to 38).

Finally, document (4) identifies melanoma-inhibitory protein (MIA) and S100 β as serum markers with almost equivalent clinical significance in staging and monitoring metastatic melanomas (page 56, right-hand column, lines 46 to 48 and page 57, right hand column. lines 2 to 17).

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 melanoma. As solutions to this problem the first searched invention provides the AKT1 gene and the second searched invention provides the MYC 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 melanoma 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, 5 and 6 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, 5 and 6 as a distinct RNA constituent" or similarly "at least 1 constituent from Tables 1, 2, 3, 4, 5 and 6 (claims 2 to 4) (emphasis added by the board). The kit of claim 24 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 23". The board therefore also concurs with the ISA that both the identified invention relating to gene AKT1 and the invention defined by the applicant with respect to the MYC gene (see Sections IV and VIII above) are subject-matter of the claimed invention.

16. 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 melanoma 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-6A 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 6, capable of distinguishing between healthy, normal subjects and melanoma 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 MYC 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