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

**Case Number:** W 0002/09 - 3.3.04

**Application Number:** PCT/US2007/023407

**Publication Number:** WO 2008/063414

**IPC:** C12Q 1/68

**Language of the proceedings:** EN

**Title of invention:**

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

**Applicant:**

Source Precision Medicine, Inc.

**Headword:**

Gene expression profiling III/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 0002/09 - 3.3.04

International Application No. PCT/US2007/023407

**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  
4 June 2008.

**Composition of the Board:**

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

## Summary of Facts and Submissions

I. International patent application no. PCT/US2007/023407 published as WO 2008/063414 and having the title "Gene expression profiling for identification, monitoring and treatment of colorectal 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 colon 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 colon 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 colon 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 colon 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 colon cancer profile based on a sample from a subject known to have colon 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 colon 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 each list numerous genes of various origin by their gene symbol (the first gene appearing in table 1 e.g. being ACSL5), their gene name (for ACSL5 e.g.: "acyl-CoA synthase long-chain family member 5") and their gene accession number (for ACSL5 e.g.: NM\_016234). The list in the tables partially overlap. Each table is labelled as a so-called "Profile". Table 1 is labelled "Precision Profile™ for Colorectal Cancer" and lists 70 genes, including the MSH6 gene.

III. On 4 June 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

three-hundred and eighty two (382) additional search fees.

IV. In the invitation to pay additional fees, the ISA defined the three-hundred and eighty three (383) inventions to which the application related as follows:

"1. claims 1-23 (partially)

INVENTION NUMBER 1:

A method for evaluating the presence of colon cancer in a subject / for assessing or monitoring the response to therapy in a subject having colon cancer / for monitoring the progression of colon cancer in a subject / for determining a colon cancer profile based on a sample from a subject known to have colon cancer, all said method being performed on a sample from said subject, as well as a kit for detecting colon cancer in said subject, all said methods and kit making use of measuring the expression of ACSL5 (the first gene listed in TABLE 1).

2. claims 1-23 (partially)

INVENTIONS NUMBER 2 - 383:

IDEM for inventions 2 - 383 starting with the gene ID mentioned in the second line of TABLE 1 and ending with the last line of TABLE 5."

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

(1) EP-A-1 512 758

(2) WO 2004/066941

(3) WO 2005/054508

(4) US 2003/054366

VI. The reasons for the finding of non-unity by the ISA was that the common concept of the application, which were differentially expressed genes qualifying as markers for colon cancer in samples from subjects suffering from this disease, the expression of these markers differing with respect to patients and reference controls, was known from the state of the art represented by documents (1) to (4).

In view of this prior art, the problem of the application was considered the provision of yet additional / alternative methods using markers for colon cancer in samples from subjects suffering from this disease, the expression of these markers differing with respect to patients and reference controls. Since the solutions that the application provides were mere alternatives to the state of the art, the ISA considered that each method and product making use of a different marker was to be considered as a separate invention. Hence, the ISA considered that the application contained three-hundred eighty three inventions as identified above.

VII. The communication dated 4 June 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 ACSL5.

- VIII. With a letter dated 3 July 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 gene MSH6.

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 colon cancer in a sample isolated from a subject. To evaluate genes capable of discriminating between healthy subjects and subjects suffering from colon 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 filed, all of the possible one- and two-gene combinations (i.e. gene models) for the genes shown in tables 1-5, capable of distinguishing between healthy, normal subjects and colon 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 of the claims with respect to all the genes listed in tables 1-5.

The applicant 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 1-5.

- IX. On 24 November 2008, 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 11 December 2008 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 ACSL5 and the invention identified by the ISA and elected by the applicant relating to the MSH6 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 ACSL5 and the invention identified by the ISA and elected by the applicant relating to the MSH6 gene as defined in the independent claims 1 (method for evaluating the presence of colon cancer in a subject), 2 (method for assessing or monitoring the response to therapy in a subject having colon cancer), 3 (method for monitoring the progression of colon cancer in a subject), 4 (method for determining a colon cancer profile based on a sample from a subject known to have colon cancer) and 23 (kit for detecting colon 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 colon 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 colorectal cancer. More specifically, the present invention relates to the use of gene expression data in the identification, monitoring and treatment of colorectal cancer and the characterization and evaluation of conditions induced by or related to colorectal 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 colon cancer was known in the state of the art.

Indeed, document (1) discloses a method of providing a prognosis of colorectal cancer based on the gene expression profiles of biological samples. This is done by an analysis of the differential modulation of the expression levels in a number of specific genes conducted by comparing such signal intensities whereby a ratio matrix of the expression intensities of genes in a test sample *versus* those in a control sample is generated (see claim 1). For instance, the gene expression intensities from a diseased tissue can be compared with the expression intensities generated from normal tissue of the same type (e.g., diseased colon tissue sample vs. normal colon tissue sample, see e.g. [0028]). Furthermore, a kit for determining the prognosis of a colorectal cancer patient, comprising materials for detecting isolated nucleic acid sequences, their complements or portions, of a combination of genes, is also provided (see claim 21).

Document (2) relates to gene expression profiles for colon cancer and uses thereof, including such methods

as a method to provide patient diagnosis (claim 1), a method to monitor the response of a patient being treated for colon cancer (claim 7) and a method for identifying a compound useful for the treatment of colon cancer (claim 10). Tables 1 to 3 identify at least 100 genes used in the profiles and their respective differential expression response.

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 colon cancer. As solutions to this problem the first searched invention provides the ACSL5 gene and the second searched invention provides the MSH6 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 colon 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, 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 ACSL5 and the invention defined by the applicant with respect to the MSH6 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 colon 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 colon cancer subjects with at least 75% classification accuracy using the claimed methods. Only for this reason therefore the further arguments of the applicant 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 MSH6 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