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Datasheet for the decision
of 27 April 2009

Case Number: W 0039/08 - 3.3.04

Application Number: PCT/US2007/023384

Publication Number: WO 2008/123866

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:
Gene expression profiling for identification, monitoring and
healment of ovarian cancer

Applicant:
Source Precision Medicine, Inc.

Headword:
Gene expression profiling II/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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Case Number: W 0039/08 - 3.3.04

International Application No. PCT/

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

Appellant:
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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:

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

Summary of Facts and Submissions

I.   International patent application no. PCT/US2007/023384
       published as WO 2008/123866 and having the title "Gene
       expression profiling for identification, monitoring and
       treatment of ovarian 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 ovarian
       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 an ovarian 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 ovarian 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

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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 ovarian
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 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 ovarian cancer profile
based on a sample from a subject known to have ovarian
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 ovarian 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 ABCB1), their gene name (for ABCB1 e.g.: "AT-binding cassette, subfamily B (MDR/TAP), member 1") and their gene accession number (for ABCB1 e.g.: NM_000927). The list in the tables partially overlap. Each table is labelled as a so-called "Profile". Table 1 is labelled "Precision Profile^{TM} for Ovarian Cancer" and lists 63 genes. Table 2 is labelled "Precision Profile^{TM} for Inflammatory Response" and lists 87 genes, including the DLC1 gene.

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 three-hundred and ninety nine (399) additional search fees.

IV.   In the invitation to pay additional fees, the ISA defined the four-hundred (400) inventions to which the application related as follows:

1. claims 1-23 (partially)

Invention Number 1:

Methods for evaluating the presence of ovarian cancer / for assessing or monitoring the response to therapy or the progression of ovarian cancer / determining an ovarian cancer profile using the expression profile of the gene ABCB1 (first gene in table 1 on page 82 of the description), as well as a kit comprising a detection or quantification means for said gene.

2. claims 1-23 (partially)

Inventions 2 - 400:

Methods for evaluating the presence of ovarian cancer / for assessing or monitoring the response to therapy or the progression of ovarian cancer / determining an ovarian cancer profile using the expression profile of the genes in tables 1 - 5 and starting with the gene ABCF2 and ending with the gene ZNF350 (last gene in table 5), as well as a kit comprising a detection or quantification means for said gene.

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

        (1)   Selvanayagam *et al.* (2004), Cancer Genetics and
               Cytogenetics, Vol. 154, No. 1, pages 63-66.

        (2)   US 2003/0180770.

        (3)   WO 2005/008213.

VI.   The reasons for the finding of non-unity by the ISA was
        that the common concept of the application, which were
        gene expression profiles associated with ovarian cancer,
        whereby at least one marker is measured and used in a
        method of either cancer detection (ovarian) or therapy
        / progression monitoring, was known from the state of
        the art represented by documents (1) to (3).

        The problem of the application was considered the
        finding and identifying yet further ovarian cancer
        markers to be used in methods of either cancer
        detection (ovarian) or therapy / progression
        monitoring. The solution then were the ovarian cancer
        markers listed in tables 1 - 5 being used in the
        methods of the application. The ISA considered the use
        of each of the ovarian cancer markers being applied in
        the methods of the application as an individual
        solution to the problem already solved in the state of
        the art in an alternative fashion. Hence, the ISA
        considered that the application contained four-hundred
        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 ABCB1.

VIII.   With a letter dated 27 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 gene DLC1.

        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 ovarian cancer in a sample isolated from a subject.
        To evaluate genes capable of discriminating between
        healthy subjects and subjects suffering from ovarian
        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 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 justified a search of 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 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 14 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 2008 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 ABCB1 and the invention identified by the ISA and elected by the applicant relating to the DLC1 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 ABCB1 and the invention identified by the ISA and elected by the applicant relating to the DLC1 gene as defined in the independent claims 1 (method for evaluating the presence of ovarian cancer in a subject), 2 (method for assessing or monitoring the response to therapy in a subject having ovarian cancer), 3 (method for monitoring the progression of ovarian cancer in a subject), 4 (method for determining a ovarian cancer profile based on a sample from a subject known to have melanoma) and 23 (kit for detecting ovarian 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 ovarian 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 ovarian cancer. More specifically,
the present invention relates to the use of gene
expression data in the identification, monitoring and
treatment of ovarian cancer and the characterization
and evaluation of conditions induced by or related to
ovarian 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 ovarian
       cancer was known in the state of the art.

       Indeed, document (1) discloses that molecular
       classification of ovarian cancer by means of
       transcription profiling has shown normal ovarian tissue
       clearly distinguishable from malignant tissues
       (page 63, right-hand column, lines 16 to 19). In
       detail, the document discloses a cDNA microarray
       examination of the expression profiles of eight primary
       ovarian cancers stratified into two groups based on
       their chemotherapeutic response. It is stated that gene
       expression profiling by means of DNA microarrays may be
       applied diagnostically for predicting treatment
       response in ovarian cancer (see abstract lines 6, 7 and
       9 to 11).

       Document (2) discloses methods for molecular
       determination whether or not a subject has ovarian
       cancer ([0021]) and the identification of markers that
       can be used to determine whether ovarian cancer is
       sensitive or resistant to a therapeutic agent ([0014],
       [0019], [0054], tables 1 and 2).

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 ovarian
        cancer. As solutions to this problem the first searched
        invention provides the ABCB1 gene and the second
        searched invention provides the DLC1 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 <u>at least one constituent</u> of any
       constituent (of any one table selected from the group
       consisting) <u>of Tables 1, 2, 3, 4 and 5</u> as a distinct
       RNA constituent" (claim 1) or similarly "determining a
       quantitative measure of the amount of <u>at least one
       constituent</u> of any constituent <u>of Tables 1, 2, 3, 4 and
       5</u> as a distinct RNA constituent" or similarly "<u>at least
       1 constituent from Tables 1, 2, 3, 4 and 5</u> (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 ABCB1 and the
       invention defined by the applicant with respect to the
       DLC1 gene (see Sections IV and VIII above) are subject-
       matter of the claimed invention, independently from
       each other.

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
       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-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 ovarian 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 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

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