PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/ES2018/070463	28.06.2018	28.06.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C12Q1/6886

Applicant
FUNDACION PARA LA INVESTIGACION BIOMEDICA DEL...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Cornelis, Karen Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/ES2018/070463

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☒ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33, 38-40
	No:	Claims	34-37
Inventive step (IS)	Yes:	Claims	1-13, 16-33, 38-40
	No:	Claims	14, 15, 34-37
Industrial applicability (IA)	Yes:	Claims	1-40
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

D1 WO 2012/067970 A2 (DAWSON TED M [US]; DAWSON VALINA L [US]; KO HAN SEOK [US]; SHIN JOOHO) 24 May 2012 (2012-05-24)

D2 T. T. VELLINGA ET AL: "SIRT1/PGC1 -Dependent Increase in Oxidative Phosphorylation Supports Chemotherapy Resistance of Colon Cancer", CLINICAL CANCER RESEARCH,
vol. 21, no. 12, 15 June 2015 (2015-06-15), pages 2870-2879, XP55523240,
US
ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-14-2290

D3 MARGALIDA TORRENS-MAS ET AL: "SIRT3 Silencing Sensitizes Breast Cancer Cells to Cytotoxic Treatments Through an Increment in ROS Production :",
JOURNAL OF CELLULAR BIOCHEMISTRY,
vol. 118, no. 2, 1 February 2017 (2017-02-01), pages 397-406, XP55524101,
ISSN: 0730-2312, DOI: 10.1002/jcb.25653

D4 WO 2012/113819 A1 (PANGAEA BIOTECH S L [ES]; TARON ROCA MIGUEL [ES]; ROSELL COSTA RAFAEL) 30 August 2012 (2012-08-30)

D5 VALERIE S. LEBLEU ET AL: "PGC-1[alpha] mediates mitochondrial biogenesis and oxidative phosphorylation in cancer cells to promote metastasis",
NATURE CELL BIOLOGY,
vol. 16, no. 10, 21 September 2014 (2014-09-21), pages 992-1003, XP55523217,
GB
ISSN: 1465-7392, DOI: 10.1038/ncb3039

D6 ALBERTO CRUZ-BERMÚDEZ ET AL: "PGC-1alpha levels correlate with survival in patients with stage III NSCLC and may define a new biomarker to metabolism-targeted therapy",
SCIENTIFIC REPORTS,
vol. 7, no. 1, 30 November 2017 (2017-11-30), XP55523682,
DOI: 10.1038/s41598-017-17009-6

Section 5

D2 discloses that in response to chemotherapy with oxiplatin colon cancer cells engage in the activation of SIRT1/PCG1alpha thereby starting OXPHOS. D2 suggests that this is the basis for the resistance to chemotherapy treatment and that this is a basis for testing if targeting the OXPHOS pathway would overcome resistance. D2 does not relate to cisplatin nor to lung cancer and the cells used in the experiments are not resistant.

D3 discloses that silencing of SIRT3 (a component of the mitochondrial OXPHOS mechanism) results in sensitivity of breast cancer cells to cisplatin (CDDP) and a reduction of the protein level of PGC-1alpha. D3 uses breast cancer instead of ling cancer and does not use PGC-1alpha as a marker.

D5 discloses that PGC-1alpha expression is linked with increased mitochondrial respiration and OXPHOS which results in breast cancer cells in increased metastasis.

D4 discloses a method to predict response of lung cancer cells to cisplatin, by detecting the expression AEG1 gene in a sample from a lung cancer patient.

Claim 1 differs from D4 in that the patient is already known to have cispaltin resistance and the expression of another gene is used as a marker. The technical effect is that the aim is to find a second treatment (which will increase the effect of the cisplatin). The problem to be solved is therefore to identify a way to overcome cisplatin resistance in lung caner patients. The solution is to determine the PGC-1alpha expression to determine if an OXPHOS blocker can be used.

Prior art D2, D3 and D5 all link PGC-1alpha to metastasis and to OXPHOS in response to treatment, however, none of these prior arts concerns lung cancer. Whilst the prior art suggest that PCG-1alpha could be a marker for OXPHOS and resistance it does not then suggest that a further compound can be supplied to these patients. Claim 1 is hence inventive.

Claim 14 does not relate to which kind of therapy is to supplied to the patient, the problem solved by claim 14 is the provision of a further marker for cisplatin resistance. Since PCG-1alpa had already been disclosed as associated with cisplatin resistance (D3) in a different kind of cancer, the subject matter of claim 14 is not considered inventive.

Since dependent claim16 includes the feature of the therapy, the subject matter of claims 16-25 is considered inventive analogously as claim 1.

Mutatis mutandis claims 26 and 38 are considered inventive.

Claim 34

The subject matter of claim 34 is a kit suitable for designing a personalised therapy. The only technical features of the kit are reagents needed to determine the expression level of the PGC-1alpha gene.

D1 discloses a kit with probes of the PCG-1alpha gene which are used to determine the expression level of PGC-1 alpha mRNA (par 274). The subject matter of claims 34-36 is therefore disclosed in D1.

Claim 37 relates to further reagents, however, all reactions of this nature require water which is one of the reagents needed to measure MIMP, ROS or mitochondrial mass. Water is usually a component of these kits. Therefore the current formulation of claim 37 is also not new.

Section 6

D6 is the publication of the application, dated after the priority date.