PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
181564WO EBO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2018/067397	28 June 2018 (28-06-2018)	29 June 2017 (29-06-2017)
Applicant		
ESSER, Knud		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out 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))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☒ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   ☐ the text is approved as submitted by the applicant
   ☒ the text has been established by this Authority to read as follows:

   METHODS FOR IDENTIFYING AGENTS WHICH INDUCE (RE) DIFFERENTIATION IN UN- OR DEDIFFERENTIATED SOLID TUMOR CELLS

5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      ☒ as suggested by the applicant
      ☐ as selected by this Authority, because the applicant failed to suggest a figure
      ☐ as selected by this Authority, because this figure better characterizes the invention
   b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2018/067397

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-18

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/067397

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/50
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HENRY WU ET AL: "Reduction in lactate accumulation correlates with differentiation-induced terminal cell division of leukemia cells*", DIFFERENTIATION., vol. 48, no. 1, 1 September 1991 (1991-09-01), pages 51-58, XP055456961, DE ISSN: 0301-4681, DOI: 10.1111/j.1432-0436.1991.tb00242.x the whole document ----- -/--	1-18

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 August 2018	05/10/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Wiesner, Martina

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JEAN-MARC BLOUIN ET AL: "Butyrate elicits a metabolic switch in human colon cancer cells by targeting the pyruvate dehydrogenase complex", INTERNATIONAL JOURNAL OF CANCER, vol. 128, no. 11, 8 October 2010 (2010-10-08), pages 2591-2601, XP055456743, US ISSN: 0020-7136, DOI: 10.1002/ijc.25599 figure 3d	1-18
Y	SANDRA VARUM ET AL: "Energy Metabolism in Human Pluripotent Stem Cells and Their Differentiated Counterparts", PLOS ONE, vol. 6, no. 6, 17 June 2011 (2011-06-17), page e20914, XP055457404, DOI: 10.1371/journal.pone.0020914 figure 3G	1-18
Y	HOFMANOVÁ JIRINA ET AL: "Lipid alterations in human colon epithelial cells induced to differentiation and/or apoptosis by butyrate and polyunsaturated fatty acids", THE JOURNAL OF NUTRITIONAL BIOCHEMISTRY, vol. 23, no. 6, 2012, pages 539-548, XP028918963, ISSN: 0955-2863, DOI: 10.1016/J.JNUTBIO.2011.02.010 Punkt 3.5; page 541	1-18
Y	HUI YAN ET AL: "Mechanism of Butyrate Stimulation of Triglyceride Storage and Adipokine Expression during Adipogenic Differentiation of Porcine Stromovascular Cells", PLOS ONE, vol. 10, no. 12, 29 December 2015 (2015-12-29), page e0145940, XP055456747, DOI: 10.1371/journal.pone.0145940 page 14, paragraph 1 - page 15, paragraph 1; figure 10	1-18

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	VALÉRIE MARCIL ET AL: "Modulation of lipid synthesis, apolipoprotein biogenesis, and lipoprotein assembly by butyrate", AMERICAN JOURNAL OF PHYSIOLOGY - GASTROINTESTINAL AND LIVER PHYSIOLOGY, vol. 283, no. 2, 1 August 2002 (2002-08-01), pages G340-G346, XP055457302, US ISSN: 0193-1857, DOI: 10.1152/ajpgi.00440.2001 the whole document	1-18
Y	NÍVEA DIAS AMOÊDO ET AL: "Energy Metabolism in H460 Lung Cancer Cells: Effects of Histone Deacetylase Inhibitors", PLOS ONE, vol. 6, no. 7, 18 July 2011 (2011-07-18), page e22264, XP055457420, DOI: 10.1371/journal.pone.0022264 page 4, right-hand column, paragraph 2 - page 6, left-hand column, paragraph 1	1-18
Y	AJANTA CHAKRABORTY ET AL: "Long term induction by pterostilbene results in autophagy and cellular differentiation in MCF-7 cells via ROS dependent pathway", MOLECULAR AND CELLULAR ENDOCRINOLOGY, ELSEVIER IRELAND LTD, IE, vol. 355, no. 1, 10 January 2012 (2012-01-10), pages 25-40, XP028475246, ISSN: 0303-7207, DOI: 10.1016/J.MCE.2012.01.009 [retrieved on 2012-01-16] page 31, right-hand column, paragraph 1	1-18
Y	PUNJ V ET AL: "EFFECT OF VITAMIN D ANALOG (1ALPHA HYDROXY D5) IMMUNOCONJUGATED TO HER-2 ANTIBODY ON BREAST CANCER", INTERNATIONAL JOURNAL OF CA, JOHN WILEY & SONS, INC, US, vol. 108, 1 January 2004 (2004-01-01), pages 922-929, XP008047279, ISSN: 0020-7136, DOI: 10.1002/IJC.11590 page 922, right-hand column, paragraph 3	1-18

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. BELFIORE ET AL: "Insulin receptor and cancer", ENDOCRINE - RELATED CANCER, vol. 18, no. 4, 23 May 2011 (2011-05-23), pages R125-R147, XP055422259, GB ISSN: 1351-0088, DOI: 10.1530/ERC-11-0074 the whole document	1-18
A	SARAH F. ANDRES ET AL: "Insulin receptor isoform switching in intestinal stem cells, progenitors, differentiated lineages and tumors: evidence that IR-B limits proliferation", JOURNAL OF CELL SCIENCE, vol. 126, no. 24, 14 October 2013 (2013-10-14), pages 5645-5656, XP055497343, GB ISSN: 0021-9533, DOI: 10.1242/jcs.132985 the whole document	1-18
A	J. HEATH: "Appearance of functional insulin receptors during the differentiation of embryonal carcinoma cells", THE JOURNAL OF CELL BIOLOGY : JCB, vol. 91, no. 1, 1 October 1981 (1981-10-01), pages 293-297, XP055497344, US ISSN: 0021-9525, DOI: 10.1083/jcb.91.1.293 the whole document	1-18

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-18

Method for the identification of compounds inducing (re-)differentiation in non- or dedifferentiated cells, comprising:a) provision of a cell culture sample consisting of de-/ or undifferentiated tumour cells,b) bringing the compound of interest into contact with the cell culture sample,c) following the determination of the relative concentration of a first marker lactate in contrast to untreated cells, andd) following the determination of the relative concentration of a second marker neutral lipids in contrast to untreated cells,wherein steps c) and d) may be performed in reverse order if necessary

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2. claim: 19

Vessel for the removal of liquids from cells via centrifugation characterized by comprising:- 4 side walls (ai, a2 , bi, b2), where the two opposing side walls have the same length (la , lb), so that a rectangular shape is obtained,- a flat bottom (c) being connected in such a way with each of the side walls over all of the connecting area in a liquid proof way,- each of the side walls having a protrusion (da , db) directed towards the inside of the vessel,- 2 of the 4 side walls being opposite to each other having recesses (ei, e2) positioned in the middle of the lengths la of the side wall on the upper surface of the respective side wall.

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3. claims: 20, 21

Microtiter plate for culturing cells enabling addition of liquid via centrifugation, said plate comprising a surface (1) and wells (2), said wells being tapered towards the bottom (3) where an opening, especially a circular opening, is present.
