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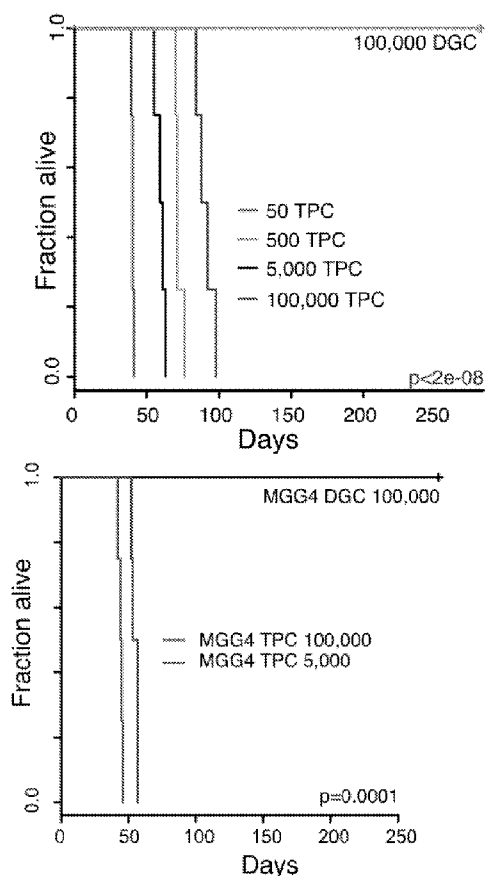
[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR DETECTING AND TREATING GLIOBLASTOMA

(57) Abstract: The present invention provides compositions and methods for the diagnosis and treatment of glioblastoma, particularly tumor propagating cells within the glioblastoma.

Figure 1

A





BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/43256

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - C12Q 1/68, G01N 33/574 (2014.01) CPC - C12Q 1/6886, A61K 38/00, C12Q 1/6883 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) IPC(8) - C12Q 1/68, G01N 33/574 (2014.01) CPC - C12Q 1/6886, A61K 38/00, C12Q 1/6883 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 435/6.14, 435/7.23, 435/6.1 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) pubWEST; Google Scholar; PatBase search terms - Glioblastoma, glioma, Astrocytoma, brain, tumor, cancer, prognos*, diagnos*, OLIG2, OLIG-2, OLIG 2, oligodendrocyte transcription factor 2, Oligodendrocyte Lineage Transcription Factor 2, PRKCBP2, BHLHB1, RACK17, Human Protein Kinase C-Binding		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0167939 A1 (ALDAPE et al.) 01 July 2010 (01.07.2010) para [0015]-[0023]; [0036]; [0044]; [0067]; [0068]; [0092]; [0093]; [0111]-[0115]; [0132]-[0150]; [0199]; [0205].	1, 3-6, (9-12)/(1,3-6), 13, 36/1, 37/1
Y		2, 7, 8, (9-12)/2
X	US 2009/0221445 A1 (WANG Y.) 03 September 2009 (03.09.2009) claims 16, 20; Table 1; para [0054].	38
Y	US 2007/0161023 A1 (PALM K.) 12 July 2007 (12.07.2007) para [0028]; [0034]; [0040]; [0044]-[0046]; [0066]-[0071].	2, 7, 8, (9-12)/2
☐ Further documents are listed in the continuation of Box C. ☐		
* 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 28 December 2014 (28.12.2014)		Date of mailing of the international search report 31 MAR 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/43256

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:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-13, 36(in part), 37(in part) and 38, directed to a tinued ipanel/method for determining the molecular profile of a glioblastoma.

Group II, claims 14-19, 36(in part) and 37(in part), directed to a method of monitoring a subject during or following treatment for glioblastom/characterizing the efficacy of a therapeutic regimen.

Group III, claims 20-27, directed to a method for obtaining an induced tumor propagating cell and the use of said cell in identifying agents that inhibit glioblastoma survival.

--continued on first blank sheet attached hereto--

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 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.:
1-13, 36-38

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.

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continuation of Box No III:

Group IV, claims 28-35, 36(in part) and 37(in part), directed to a method for treating a subject diagnosed as having a glioblastoma/for reducing the survival or proliferation of a subpopulation of tumor propagating cells present in a glioblastoma.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special technical features

Group I includes the special technical feature of a method/panel for determining the molecular profile of a glioblastoma, which is not required by Groups II-IV.

Group II includes the special technical feature of a method of monitoring a subject during or following treatment for glioblastoma, which is not required by Groups I, III or IV.

Group III includes the special technical feature of a method for obtaining an induced tumor propagating cell, the method comprising recombinantly expressing LSD1, RCOR2, POU3F2, SOX2, SALL2, and/or OLIG2 in a cell, thereby obtaining an induced tumor propagating cell, which is not required by Groups I, II or IV.

Group IV includes the special technical feature of a method for treating a subject diagnosed as having a glioblastoma, a method for reducing the survival or proliferation of a subpopulation of tumor propagating cells present in a glioblastoma, the method comprising contacting the cells with an agent that inhibits POU3F2, SOX2, SALL2, OLIG2, RCOR2 and/or LSD1, thereby inhibiting the survival or proliferation of said subpopulation of tumor propagating cells present in a glioblastoma, which is not required by Groups I-III.

Common technical features

Groups I-IV share the technical feature of LSD1, RCOR2, POU3F2, SOX2, SALL2, and/or OLIG2 expression in a cell related to tumor propagation/growth present in a glioblastoma. Groups I and II further share the technical feature of a method of measuring the levels of LSD1, RCOR2, POU3F2, SOX2, SALL2, and/or OLIG2 proteins or a nucleic acid molecule encoding said proteins in a biologic sample from a subject relative to the levels in a reference, wherein said levels are related to glioblastoma status. Groups III and IV further share the technical feature of tumor propagating cells.

However, these shared technical features do not represent a contribution over prior art, because these shared technical features are anticipated by US 2010/0167939 A1 to Aldape et al., (hereinafter Aldape).

Aldape teaches a method for determining the molecular profile of a glioblastoma, the method comprising measuring the levels of OLIG2 protein or a nucleic acid molecule encoding said protein in a biologic sample from a subject (para [0015], [0017]-[0019]), relative to the levels in a reference (para [0015]), wherein said levels are related to glioblastoma status (para [0015]).

Aldape further teaches tumor propagating cells (para [0149] glioblastoma tumor cells with malignant potential comprise tumor propagating cells).

Therefore, Groups I-IV lack unity of invention under PCT Rule 13.

NOTE:

Claim 25 refers to "induced tumor propagating cell of claim 10" which lacks antecedent. For the purpose of this invitation, claim 25 is interpreted as incorporating "the induced tumor propagating cell obtained by the method of claim 20."