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- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, 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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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

[Continued on next page]

- (54) **Title:** METHODS AND COMPOSITIONS FOR THE TREATMENT OF CANCER

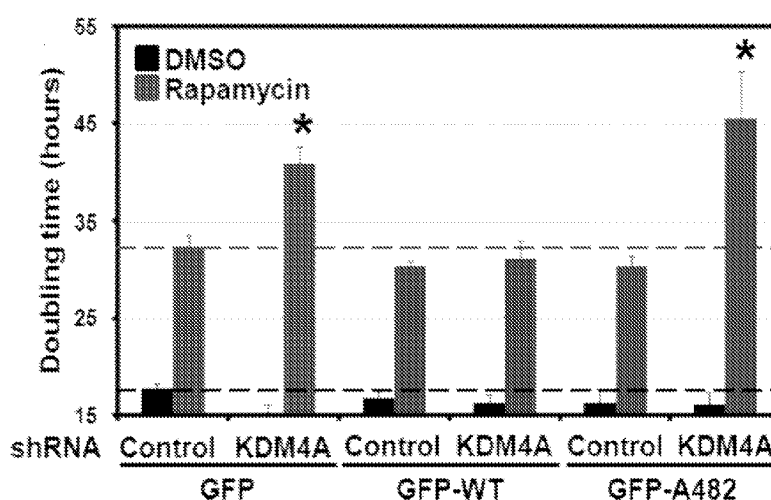


Figure 18

- (57) **Abstract:** The methods and uses described herein relate to the role of KDM4A in, e.g. cancer, and permit, e.g. the diagnosis, prognosis, and treatment of cancer and graft vs. host disease.



— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:

26 February 2015

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/41359

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12Q 1/68, A61P 35/00 (2014.01)

CPC - C12Q 2600/106, C12Q 1/6886

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, A61P 35/00 (2014.01)

CPC: C12Q 2600/106, C12Q 1/6886

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC: C12Q 1/68

(keyword limited; terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar, Google Web, search terms: KDM4A or JMJD2A or Lysine-specific demethylase 4A, cancer or tumor or malignancy, hypoxic tumor S-phase chemotherapy, mTOR inhibitors; protein synthesis inhibitors, VEGFR inhibitors, lq21.2, lq12h, or Xq12.1, HIF1 alpha, STAT3, HDAC, cisplatin, 5-fluorouracil, gene amplification, suc

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2011/0172107 A1 (KATZ et al.) 14 July 2011(14.07.2011) para [0013], [0018], [0077], [0107]	18, 19, 63, 64 ----- 20, 65
X --- Y	SHANNON et al., Tumour hypoxia, chemotherapeutic resistance and hypoxia-related therapies. Cancer Treatment Reviews, August 2003, vol 29, no 4, pp 297-307, pg 297, col 2, para 2- pg 298, col 1-2, pg 299 col 1, para 1, pg 301, col 1, para 2-3, pg 303 col 2, para 2	1-3, 46-49 ----- 4-6, 25, 50-52, 68
X --- Y	WO 2012/037212 A1 (PRICE et al.) 22 March 2012 (22.03.2012) pg 22, para 2 - pg 23, para 1	24, 67 ----- 25, 68
Y	BLACK et al. Conserved Antagonism between JMJD2A/KDM4A and HP1.gamma. during Cell Cycle Progression. Molecular Cell, 10 December 2010, Vol 40, No 5, pp 736-748, pg 739, col 1, para 1 - col 2, para 1, pg 744 col 2, para 2, Fig. 1F	4-6, 50-52
Y	US 2012/0214757 A1 (ANDERSON et al.) 23 August 2012 (23.08.2012) para [0009], [0060]	20, 65
A	COLLINS et al. Transcriptional Consequences of Topoisomerase Inhibition. Mol Cell Biol, December 2001, vol 21, no 24, pp 8437-8451, abstract	3, 47

☐ 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

11 December 2014(11.12.2014)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/41359

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.: 7-17, 21-23, 26, 34-45, 53-62, 66, 69, 73, 81-89
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 1-6, 18-20, 24-25, 46-52, 63-65, 67-68, drawn to methods of treating cancer and uses of chemotherapeutic and/or KDM4A modulating compositions for the treatment of cancer

Group II: Claims 27-29, drawn to an assay for determining the likelihood of a subject experiencing a positive outcome following treatment for cancer

Group III: Claims 30-33, 70-72, drawn to methods for treating graft versus host disease

Group IV: Claims 74-80, drawn to methods and assays for diagnosing or treating autism or schizophrenia
---please see extra 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 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.:
1-6, 18-20, 24-25, 46-52, 63-65, 67-68

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/US 14/41359

Continuation of Box No. III Observations where unity of invention is lacking

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 requires methods and uses for treatment of cancer, not required by Groups II-IV.

Group II requires a method of predicting the outcome of cancer treatment, and determining the level or mutational status of KDM4C or KDM4D, not required by Groups I and III-IV.

Group III requires the treatment of graft versus host disease, not required by Groups I-II and IV.

Group IV requires the treatment or diagnosis of autism or schizophrenia, not required by Groups I-III.

Common Technical Features

The feature shared by Groups I-IV is a KDM4A dampening mutation. Further, the feature shared by Groups I and IV is an agonist of KDMA4. However, these shared technical features do not represent a contribution over prior art, because the shared technical features are taught by the article entitled "Conserved Antagonism between JMJD2A/KDM4A and HP1.gamma. during Cell Cycle Progression" by Black et al. (Molecular Cell, 10 December 2010, Vol 40, No 5, pp 736-748) (hereinafter 'Black'). Black discloses a KDM4A dampening mutation (p739, col 2, para 1 - "catalytically inactive JMJD2A.sup.H188A", note that JMJD2A is also known as KDM4A). Black further teaches a method of ectopically expressing JMJD2A/KDMA4, thereby overexpressing JMJD2A/KDMA4 (p 737, col 2, para 2 - "We ectopically expressed JMJD2A to determine its effect on cell cycle progression (Figure 1B). We created stable HEK293T cells expressing ... JMJD2A ... These cell lines exhibited modest 2- to 3-fold overexpression of ... JMJD2A ... Interestingly, ectopic expression of JMJD2A resulted in stabilization of both endogenous and exogenous JMJD2A throughout the cell cycle"; p 746, col 2, para 3, retroviral expression vectors for infecting cells to produce JMJD2A overexpressing stable cell lines, the vectors representing "agonists" of JMJD2A /KDMA4 that increase JMJD2A/KDMA4 activity and expression). As the technical feature was known in the art at the time of the invention, it cannot be considered a special technical feature that would otherwise unify the groups.

The feature shared by Groups I -II is the association between altered expression levels of KDM4A and cancer. Another feature shared by Groups I and III is an inhibitor of KDMA4. However, these shared technical features do not represent a contribution over prior art, because the shared technical features are taught by the article entitled "KDM4/JMJD2 histone demethylases: epigenetic regulators in cancer cells" by Berry et al. (Cancer Res. 15 May 2013, Vol 73, No 10, pp 2936-42) (hereinafter 'Berry'). Berry discloses that KDM4A is shown to be overexpressed in breast, colorectal, lung, prostate, and other tumors and are required for efficient cancer cell growth (abstract). Berry further teaches an inhibitor of KDMA4 (abstract - "HP1.gamma. antagonized JMJD2A [KDM4]-dependent progression through S phase"). As the technical feature was known in the art at the time of the invention, it cannot be considered a special technical feature that would otherwise unify the groups.

The feature shared by Groups I and III is an mTOR inhibitor. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is taught by US 2011/0195966 A1 to Garcia-Echeverria et al. (hereinafter 'Garcia-Echeverria'). Garcia-Echeverria discloses an mTOR inhibitor (abstract, para [0007], pharmaceutical composition comprising mTOR inhibitor) that can be used for treatment (para [0011] - "use for the treatment of mammalian target of rapamycin (mTOR) kinase dependent diseases") cancers (para [0154]) as well as graft-verus-host disease (para [0129]-[0130]). As the technical feature was known in the art at the time of the invention, it cannot be considered a special technical feature that would otherwise unify the groups.

Groups I-IV therefore lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.