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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))*

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))*

(88) Date of publication of the international search report:
9 April 2015

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(54) Title: COMPOSITIONS AND METHODS FOR MODULATING DNA METHYLATION

(57) Abstract: Disclosed herein are compositions and methods for modulating DNA methylation of one or more gene promoters, treating a subject diagnosed with or suspected of having a disease or disorder characterized by DNA hypermethylation, decreasing c-myc expression, increasing desmoplakin expression, and inhibiting metastases.

INTERNATIONAL SEARCH REPORT

~~PCT/US14/51317 18.02.2015~~
International application No.
PCT/US 14/51317

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/40, A61K 31/44, C12N 5/00 (2015.01)
CPC - C07D 213/82, C07D 213/81, A61K 38/00
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): A01N 43/40, A61K 31/44, C12N 5/00 (2015.01)
CPC: C07D 213/82, C07D 213/81, A61K 38/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/350, 514/354, 435/375 (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: HIF alpha, HIF beta, prolyl hydroxylase inhibitor, DNA demethylase, promoter methylation cancer, 5mC hydroxylase, 5mC methylase, PHD2, PHD3, EGLN2, EGLN3, 2-HG, IDH1, VEGF-A, desmoplakin, DSP, methylation status, hypermethylation, hypomethylation,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	US 2010/0331374 A1 (WU et al.) 30 December 2010 (30.12.2010) para [0003], [0006], [0011], [0014], [0298], [0301], [0303], [0331], [0351], [0357]	1-10, 13-37, 40-61, 64-76 --- 11, 12, 38, 39, 62, 63
Y	Liu et al. Hypoxia Induces Genomic DNA Demethylation through the Activation of HIF-1alpha and Transcriptional Upregulation of MAT2A in Hepatoma Cells. Mol Cancer Ther (June 2011) vol 10 pp 1113-1123, abstract, pg 1114, col 1, para 2, pg 1116, col 2, para 1, pg 1121, col 2, para 4, pg 1122, col 1, para 1, col 2, para 1	1-10, 13-37, 40-61, 64-76
Y	US 2013/0022974 A1 (Chinnaiyan et al.) 24 January 2013 (24.01.2013) para [0008], [0010], [0014], [0015], [0027], [0027], [0051], [0052], [0055], [0065], [0066], [0100], Figs. 5, 18	1-10, 13-37, 40-61, 64-76
Y --- A	US 2012/0329836 A1 (MARSH et al.) 27 December 2012 (27.12.2012) para [0002], [0213]	14, 16, 41, 43, 65, 67 --- 11, 12, 38, 39, 62, 63
Y	Yang et al. Desmoplakin acts as a tumor suppressor by inhibition of the Wnt/beta-catenin signaling pathway in human lung cancer. Carcinogenesis (12 July 2012) vol 33, no 10, pp 1863-1870, pg 1863, col 1, para 2 - col 2, para 1-2, pg 1865, col 1, para 4, pg 1868, col 1, para 4 - col 2, para 1, Fig 2	17, 21-25, 44, 46-50, 71-75

☐ 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	Date of mailing of the international search report
28 January 2015 (28.01.2015)	18 FEB 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 14/51317

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 1-76, drawn to a method of modulating DNA methylation of one or more gene promoters in a subject and a method for treating a subject diagnosed with or suspected of having a disease or disorder characterized by DNA hypermethylation.

Group II: claims 77-90, drawn to a method for decreasing c-myc expression in a subject.

Group III: claims 91-108, drawn to a method for increasing desmoplakin expression in a subject.

Group IV: claims 109-123, drawn to a method for treating cancer and inhibiting metastases in a subject.

********** See extra sheet to continue **********

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.:
1-76

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.

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

The inventions listed as Groups I through 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

The special technical feature of each of Groups I-IV is a method of treating a unique disorder in a subject, as outlined above.

Common Technical Features

The inventions of Groups I-IV share the technical feature of a method of treating a disorder in a subject, comprising: administering to a subject an effective amount of composition comprising a compound of {[5-(3-Fluorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid, or a pharmaceutically acceptable salt thereof.

However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2010/0331374 A1 by Wu et al. (hereinafter 'Wu'). Wu teaches a method of treating a disorder in a subject (para [0006], [0010]), comprising: administering to a subject an effective amount of composition (para [0008]) comprising a compound of {[5-(3-Fluorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid (para [0193], Table III, compound 67), or a pharmaceutically acceptable salt thereof (para [0007]). As said technical feature was known in the art at the time of the invention, this cannot be considered special technical feature that would otherwise unify the groups.

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