(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 August 2016 (04.08.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/123054 A3

(51) International Patent Classification:
G01N 33/574 (2006.01) *C12Q 1/68* (2006.01)
A61K 39/00 (2006.01)

(21) International Application Number:
PCT/US2016/014831

(22) International Filing Date:
26 January 2016 (26.01.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/107,788	26 January 2015 (26.01.2015)	US
62/144,457	8 April 2015 (08.04.2015)	US
62/195,435	22 July 2015 (22.07.2015)	US

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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, 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.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

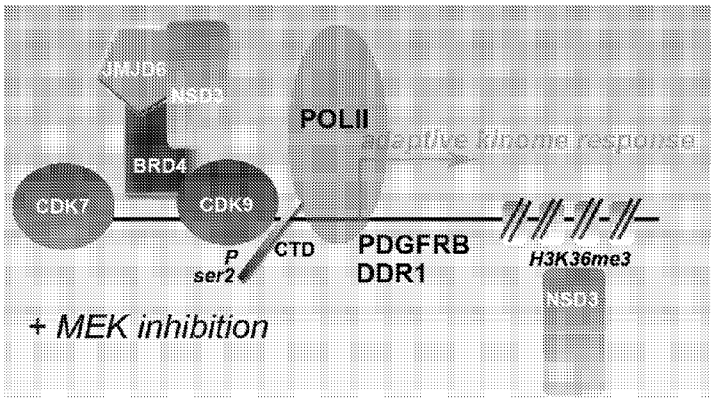
Published:

— *with international search report (Art. 21(3))*

[Continued on next page]

(54) Title: KINASE DRUG COMBINATIONS AND METHODS OF USE THEREOF

FIG. 4



(57) Abstract: The present disclosure relates to method for inhibiting cancer cell growth or inducing apoptosis in cancer cells by inhibiting kinome reprogramming in a combination therapy involving kinase inhibitors. A kinase inhibitor in combination with a P-TEFb inhibitor and/or p300/CBP inhibitor provides a stable growth suppression of the cancer cells, blocking kinome reprogramming response to kinase inhibitors.

WO 2016/123054 A3

— *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:
20 October 2016

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/14831

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.: 58-61
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:

-***-Continued Within the Next Supplemental Box-***-

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.:
1-27, 29-43, 47-53, 56, 57

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/US16/14831

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 33/574; A61K 39/00; C12Q 1/68 (2016.01)
CPC - G01N 33/53; C12N 15/115; 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) Classification(s): G01N 33/574; A61K 39/00; C12Q 1/68; CPC Classification(s): G01N 33/53; C12N 15/115; C12Q 1/6886

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)
USPTO Web Page; PatSeer (US, EP, WO); Google; Google Scholar; EBSCO; Entrez Pubmed; Science Direct; Search terms -- cancer, growth, apoptosis, "kinase inhibitor", "P-TEFb inhibitor", "CBP/p300 inhibitor", kinome, "kinase signaling", CDK9, BRAF, VEGF, MAP kinase, gemcitabine, BRD4

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 2013/148114 A1 (UNIVERSITY OF FLORIDA RESEARCH FOUNDATION, INC.) October 3, 2013; abstract; page 4, lines 5-19; page 5, lines 18-23; page 8, line 25 -- page 9, line 5; page 9, lines 14-20, lines 28-32; page 16, lines 9-10, lines 32-33; page 17, lines 1-5; page 31, lines 25-28; page 34, lines 1-2; figure 4	3, 5/3, 13/5/3, 14/5/3, 15/5/3, 16/5/3 ---------- 1-2, 4/1-2, 5/1, 6/1-2, 7/6/1-2, 8/7/6/1-2, 9/1-2, 10/9/2, 11/10/9/1-2, 12/1-2, 13/5/1, 14/5/1, 15/5/1, 16/5/1, 17/12/1-2, 18/12/1-2, 19/18/12/1-2, 20/18/12/1-2, 21/12/1-2, 22/12/1-2, 23/12/1-2, 24/12/1-2, 25/12/1-2, 26-27, 29/26-27, 30/29/26-27, 31/29/26-27, 32-36, 37/35-36, 38-43, 47-53, 56-57

☒ 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 May 2016 (06.05.2016)	19 AUG 2016

Name and mailing address of the ISA/	Authorized officer
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/14831

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0215793 A1 (MICHELSON, GC et al.) August 27, 2009; abstract; paragraphs [0001], [0126], [0244], [0245], [0247]	1, 4/1, 5/1, 6/1, 7/6/1, 8/7/6/1, 9/1, 10/9/1, 11/10/9/1, 12/1, 13/5/1, 14/5/1, 15/5/1, 16/5/1, 17/12/1, 18/12/1, 19/18/12/1, 20/18/12/1, 21/12/1, 22/12/1, 23/12/1, 24/12/1, 25/12/1, 26, 29/26, 30/29/26, 31/29/26, 32-35, 37/35, 38-43, 47-53, 56-57
Y	WO 2013/026890 A1 (LEAD DISCOVERY CENTER GMBH) February 28, 2013; abstract; page 1, lines 10-13; page 3, lines 25-34; page 6, lines 21-24; page 8, lines 18-24; page 50, lines 22-23; page 51, line 10; page 79, lines 20-26; page 80, lines 34-35; page 81, line 20	2, 4/1-2, 6/1-2, 7/6/1-2, 8/7/6/1-2, 9/1-2, 10/9/1-2, 11/10/9/1-2, 12/2, 17/12/2, 18/12/2, 19/18/12/2, 20/18/12/2, 21/12/2, 22/12/2, 23/12/1-2, 24/12/2, 25/12/2, 27, 29/26-27, 30/29/27, 31/29/27, 34-36, 37/35-36, 41-43, 47-49, 52-53, 56-57
Y	WO 2012/138739 A2 (CHEMOENHANCED, LLC) October 11, 2012; abstract; page 2, lines 9-17; page 20, lines 1-7; page 22, lines 8-13	17/12/1-2, 20/18/12/1-2
Y	US 2010/0168228 A1 (BOSE, JS et al.) July 1, 2010; paragraphs [0002], [0089], [0145]	39-40, 42-43, 48-49

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US16/14831

-***-Continued from Box III: Lack of Unity of Invention-***-

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 1-27, 29-31, 32 (in-part), 33 (in-part), 34 (in-part), 35-43, 47-53, 56 and 57 are directed toward methods including administering to a cancer cell or patient a CBP inhibitor, a p300 inhibitor, or a CBP/p300 inhibitor and/or a P-TEFb inhibitor and/or a kinase inhibitor.

Group II, Claims 28, 32 (in-part), 33 (in-part), 34 (in-part), 44-46, 54 and 55 are directed toward methods including administering to a cancer cell or patient a CBP inhibitor, a p300 inhibitor, or a CBP/p300 inhibitor and a chemotherapeutic compound, wherein said chemotherapeutic compound is a nucleotide analog.

The inventions listed as Groups I and II 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: the special technical features of Group I include a compound that inhibits the activity of positive transcription elongation factor b (PTEFb), not present in Group II; the special technical features of Group II include a chemotherapeutic compound, wherein said chemotherapeutic compound is a nucleotide analog, not present in Group I (the recitation of a chemotherapeutic compound within Group I is optional and not required).

Groups I and II share the technical features including: dysregulation of a kinase signaling network; a method for inducing apoptosis in a cancer cell comprising administering to the cancer cell a CBP inhibitor, a p300 inhibitor, or a CBP/p300 inhibitor; a method of treating a subject with a cancer, the method comprising (i) administering to the subject a compound that inhibits the activity of CBP and/or p300; a method of reducing the proliferation rate of a cancer cell population, the method comprising (i) administering to the cancer cell population a compound that inhibits the activity of CBP and/or p300; and a method of enhancing the rate of apoptosis in a cancer cell population, the method comprising (i) administering to the cancer cell population a compound that inhibits the activity of CBP and/or p300.

However, these shared technical features are previously disclosed by WO 2013/148114 A1 to University of Florida Research Foundation Inc. (hereinafter 'Florida').

Florida discloses dysregulation of a kinase signaling network (wherein a JAK2/STAT3 kinase pathway is preferentially active in breast cancer cells (dysregulation of a kinase signaling network); page 3, lines 3-7); a method for inducing apoptosis in a cancer cell (a method for inducing apoptosis in chemotherapy resistant breast cancer cells using a p300 inhibitor, L002 (a method for inducing apoptosis in a cancer cell); page 3, lines 25-31; page 4, lines 31-33; page 5, lines 18-23; page 16, lines 5-10) comprising administering to the cancer cell (comprising administering to the cancer cell; page 31, lines 4-12) a p300 inhibitor (a p300 inhibitor, L002 (page 4, lines 31-33; page 31, lines 4-12); a method of treating a subject with a cancer (a method of treating a subject with a cancer; page 9, lines 6-13), the method comprising (i) administering to the subject a compound (the method comprising (i) administering to the subject L002 (a compound); page 9, lines 6-13) that inhibits the activity of p300 (that inhibits the activity of p300; page 4, lines 31-33); a method of reducing the proliferation rate of a cancer cell population (a method of reducing the proliferation rate of a cancer cell population; page 9, lines 28-32), the method comprising (i) administering to the cancer cell population a compound (the method comprising (i) administering to the cancer cell population L002 (a compound); page 9, lines 28-32) that inhibits the activity of p300 (that inhibits the activity of p300; page 4, lines 31-33); and a method of enhancing the rate of apoptosis in a cancer cell population (a method for inducing apoptosis in chemotherapy resistant breast cancer cells using a p300 inhibitor, L002 (a method of enhancing the rate of apoptosis in a cancer cell population); page 3, lines 25-31; page 4, lines 31-33; page 5, lines 18-23; page 16, lines 5-10), the method comprising (i) administering to the cancer cell population a compound (the method comprising (i) administering to the cancer cell population L002 (a compound); page 31, lines 4-12) that inhibits the activity of p300 (that inhibits the activity of p300; page 4, lines 31-33).

Since none of the special technical features of the Groups I and II inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Florida reference, unity of invention is lacking.