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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 December 2016 (15.12.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/201450 A3

(51) **International Patent Classification**:
A61K 48/00 (2006.01) *C12Q 1/68* (2006.01)
A61K 39/00 (2006.01) *G01N 33/00* (2006.01)
A61P 35/00 (2006.01)

(21) **International Application Number**:
PCT/US2016/037288

(22) **International Filing Date**:
13 June 2016 (13.06.2016)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
62/174,374 11 June 2015 (11.06.2015) 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))*

— *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))*

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

(88) **Date of publication of the international search report**:
19 January 2017

WO 2016/201450 A3

(54) **Title**: CANCER TREATMENT AND DIAGNOSIS

(57) **Abstract**: The present disclosure provides, in general, a method for selecting a therapy for treating cancer in a human subject and subsequently treating cancer in a subject, which includes isolating a cancer cell from a human subject having cancer, determining the functional activity of STING or cGAS in the cell; and selecting a therapy for the cancer based on the functional activity of the STING or cGAS in the cell. Also provided, if the functional activity of STING and/or cGAS is determined to be defective in the cell, the therapy selected is one that is effective at killing STING-deficient and/or cGAS-deficient cancer cells, e.g., therapy including administering to the subject an oncolytic virus.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/37288

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 48/00; A61K 39/00; A61P 35/00; C12Q 1/68; G01N 33/00 (2016.01)

CPC - C12N 15/86; A 61K 38/00; A61K 39/00; C12Q 1/6883; C12Q 1/686; G01N 33/57

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) - A61K 48/00; A61K 39/00; A61P 35/00; C12Q 1/68; G01N 33/00 (2016.01); USPC - 424/93.2,184.1; 514/19.3; 435/6.11,6.12,7.92
CPC - C12N 15/86; A 61K 38/00; A61K 39/00; C12Q 1/6883; C12Q 1/686; G01N 33/57

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 48/00; A61K 39/00; A61P 35/00; C12Q 1/68; G01N 33/00 (2016.01); USPC - 424/93.2,184.1; 514/19.3; 435/6.11,6.12,7.92
CPC - C12N 15/86; A 61K 38/00; A61K 39/00; C12Q 1/6883; C12Q 1/686; G01N 33/57 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); PatBase; Medline, Google: STING, stimulator of interferon genes, TMEM17, MPYS, MITA, ERIS, Cyclic GMP-AMP synthase, cGAS, cGAMP synthase, treating, cancer, colorectal, colitis, melanoma, oncolytic virus, herpes simplex virus, HSV, vaccinia, Varicella Zoster, killing, chemotherapy, resistant, fail, DNA, gene, mutation,

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 2013/0039933 A1 (Barber) 14 February 2013 (14.02.2013), para [0002], [0005], [0021], [0025], [0036], [0090], [0091], [0104], [0112], [0113], [0114], [0118], [0145], [0159], [0171], [0215], [0309], [0313], [0314], and [0373]	1, 14/(1) --- 2-13, 14/(2-13)
Y	US 2009/0317456 A1 (KARRASCH et al.) 24 December 2009 (24.12.2009), para [0003], [0004], [0016], [0038], [0050], [0063], [0132], [0161], and [0267]	2, 5-6, 8-9, 12-13, and 14/(2, 5-6, 8-9, 12-13)
Y	US 2013/0039890 A1 (ARCH DEVELOPMENT CORPORATION et al.) 14 February 2013 (14.02.2013),Abstract, para [0004], [0007], [0009], [0022], [0030], and [0033]	3-4, 14/(3-4)
Y	KATO et al., Structural and Functional Analyses of DNA-Sensing and Immune Activation by Human cGAS. PLoS One. 2013, Vol. 8(10):e76983. PDF File: pg 1-9. Abstract; pg 7, Fig 4; and pg 8, col 1, middle para	7, 9, 11-13, 14/(7, 9, 11-13)
Y	US 2004/0024063 A1 (Berge) 05 February 2004 (05.02.2004), para [0001], [0022], [0038], [0040], [0059], [0065], and [0084]	10, 14/(10)
A	US 2015/0087973 A1 (Peyman) 26 March 2015 (26.03.2015), para [0003]	1-14
A	CAI et al., The cGAS-cGAMP-STING Pathway of Cytosolic DNA Sensing and Signaling. Mol Cell. 2014, Vol. 54(2), p. 289-96. Entire documentation, especially Abstract; pg 290, Fig 1; and pg 294, col 1, last para	1-14
A	WO 2014/099824 A1 (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 26 June 2014 (26.06.2014), Abstract, para [003], [017], [022], [027], and [028]	1-14

☐ 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
13 October 2016	30 NOV 2016
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. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/37288

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.: 15-19
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.

Groups I+, Claims 1-14, directed to a method for treating cancer in a (human) subject. The determination step will be searched to the extent that the determination step encompasses determining the functional activity of stimulator of interferon genes (STING) in the sample; the selection step will be searched to the extent that the selection step encompasses selecting a therapy for the cancer based on the functional activity of the STING in the sample; and treatment step will be searched to the extent that the treatment step encompasses if the sample has defective STING activity, administering an oncolytic virus to the subject. It is believed that claims 1-9, 12 -13 (in part), and 14/[1-9, 12-13(in part)] encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass determining the functional activity of STING in the sample; selecting a therapy for the cancer based on the functional activity of the STING in the sample; and if the sample has defective STING activity, administering an oncolytic virus to the subject. **********Continued in the 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.:

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 16/37288

Continuation of:
Box No III (unity of invention is lacking)

(Continuation of Groups I+) Additional determination step(s), selection step(s), and/or treatment step(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected determination step(s), selection step(s), and/or treatment step(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be: 1) the determination step encompasses determining the functional activity of stimulator of interferon genes (STING) in the sample; and the selection and treatment steps encompasses if the sample does not have defective STING activity, administering a cancer treatment to the subject that does not cause DNA mutation [claims (1), (3-4), (7), 10, and 14/[(1),(3-4),(7),10]; or 2) the determination step encompasses determining the functional activity of cyclic GMP-AMP synthas (cGAS) in the sample, and the selection step encompasses selecting a therapy for the cancer based on the functional activity of the cGAS in the sample {Claims 11, 12-13(in part), and 14/[11, 12-13 (in part)]}.

The inventions listed as Groups I+ 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 Feature
Among Groups I+, 'an oncolytic virus' administered under the condition of 'if the sample has defective STING activit' in claims 1-9, 12-13 (in part), and 14/[1-9, 12-13(in part)], is structurally and functionally different from 'a cancer treatment to the subject that does not cause DNA mutation', administered under the condition of 'if the sample does not have defective STING activity' in claims 10 and 14/(10);
--a method for 'determining the functional activity of STING in the sample' in claims 1-10, 12-13 (in part), and 14/[1-10, 12-13(in part)], requires different technologies and reagents for detection comparing with a method for 'determining the functional activity of cGAS in the sample' in claims 11, 12-13(in part), and 14/11, 12-13 (in part)], and vice versa; and
--the therapeutic agents selected based on 'selecting a therapy for the cancer based on the functional activity of the STING in the sample' in 1-10, 12-13 (in part), and 14/[1-10, 12-13(in part)], are structurally and functionally different from the therapeutic agents selected based on 'selecting a therapy for the cancer based on the functional activity of the cGAS in the sample' in claims 11, 12-13(in part), and 14/[11, 12-13 (in part)], because of a different target, STING or cGAS is targeted.

Common Technical Features
The inventions of Groups I+ shared technical features of:
-- a method for treating cancer in a human subject, the method comprising the steps of: isolating a sample from a human subject having cancer; determining the functional activity of stimulator of interferon genes (STING) in the sample; selecting a therapy for the cancer based on the functional activity of the STING in the sample; and treating the subject with the selected therapy (claim 1); and
--claims 10 and claim 12 and their dependent claims further share the technical feature of a sample (from a cancer patient) does not have defective STING activity, administering a cancer treatment to the subject (claim 10: administering a cancer treatment to the subject that does not cause DNA mutation; claim 12: administering a second agent).

However, these shared technical features do not represent a contribution over prior art as being anticipated by US 2013/0039933 A1 to Barber; or as being obvious over Barber as follows:

Barber discloses a method for treating cancer in a human subject (para [0002] - 'modulating innate and adaptive immunity in a subject ... for the treatment of an immune-related disorder, cancer'; para [0091] - 'a mammalian subject to be treated, with human patients being preferred'), the method comprising the steps of:
--isolating a sample from a human subject having cancer (para [0314] - 'a cell from a patient is isolated'; para [0113] - 'patients for the treatment of cancer'; para [0090] - 'A sample comprising polynucleotides, polypeptides, ...may comprise a bodily fluid; a soluble fraction of a cell preparation'; para [0091] - 'patient ... with human patients being preferred');
--determining the functional activity of stimulator of interferon genes (STING) in the sample (para [0118] - 'STING is a prognostic marker for disease progression or outcome or response or resistance to anti-cancer therapies. ... loss of STING, change in expression and/or function of STING as compared to a normal cell'; para [0005] - 'STING molecules (Stimulator of Interferon Genes)'; para [0309] - 'measuring functions of STING, ... STING mediated interferon induction...the cells are contacted with a cDNA or a random peptide library'; para [0159] - 'plasmid DNA completely fails to activate IFN in the absence of STING'; para [0314] - 'a cell from a patient is isolated'; para [0113] - 'patients for the treatment of cancer'; para [0090] - 'sample comprising ... a cell preparation');
--selecting a therapy for the cancer based on the functional activity of the STING in the sample (para [0118] - 'STING is a prognostic marker for disease progression ... anti-cancer therapies. ... loss of STING, change in ... function of STING as compared to a normal cell, or detection of a mutant STING ...cell progressing towards being a tumor cell'; para [0036] - 'STING is lost from numerous cancer cells ... reconstitution of STING can rescue the intracellular DNA-mediated type I IFN induced pathway'; para [0112] - 'treatment of cancer comprises administration of STING or agents which induce STING and pathways'; para [0313] - 'diagnosis and candidate drug discovery includes contacting a test sample with a cell expressing STING ... and detecting interaction of the test sample with STING'; para [0314] - 'a cell from a patient is isolated'; para [0090] - 'sample comprising ... a cell preparation'); and
--treating the subject with the selected therapy (para [0112] - 'treatment of cancer comprises administration of STING or agents which induce STING and pathways thereof. ...evidences that the intracellular DNA pathway that is regulated by STING is defective in all cancer cells examined so far'; para [0113] - 'STING and/or STING interacting molecules are administered to patients for the treatment of cancer. STING can be administered as a polynucleotide, polypeptide,... vectors expressing STING, ... defective intracellular DNA signaling in cancer cells but not normal cells. Thus, reconstitution of STING and/or STING associated molecules are used in treatments for cancer'; [0373] - 'in the case of cancer, the STING compositions can be administered with chemotherapeutic or surgical treatments').

**********Continued in the next extra sheet**********

Continuation of:
The previous extra sheet - Box No III (unity of invention is lacking)

Barber further discloses cancer cell may activate STING pathway (para [0111] - 'STING induces an anti-tumor response. Cancer cells may activate the STING pathway by numerous ways'), indicating cancer sample (from a cancer patient) does not have defective STING activity. Although Barber does not expressively teach administering a cancer treatment to the subject, 'if a sample does not have defective STING activity', one of the ordinary skill in the art at the time the invention was made would have known to do so, because Barber further discloses STING is required for in vivo host defense by producing interferon (IFN) (para [0021] - 'STING is required for effective in vivo host defense'; para [0025] - 'Defective type I IFN production in viral-infected STING knockout mice'; para [0145] - 'interferon (IFN)'), and provides therapeutic agents including activators and inhibitors of STING for treating cancer (para [0113] - 'STING and/or STING interacting molecules are administered to patients for the treatment of cancer. STING can be administered as a polynucleotide, polypeptide, peptides, antisense oligonucleotides, vectors expressing STING, antibodies and the like'; para [0363] - 'provided a compound for use in a medicament...treating diseases...by modulating the immune response e.g. cancer...STING may be down-regulated, e.g. antisense, siRNA, antibodies'; para [0112] - 'treatment of cancer comprises administration of STING or agents which induce STING and pathways thereof. ...evidences that the intracellular DNA pathway that is regulated by STING is defective in... cancer cells'). Therefore, one of the ordinary skill in the art at the time the invention was made would have known to select therapeutic agents for administering a cancer treatment to the subject, 'if a sample does not have defective STING activity', in order to modulate STING activity to a desired level based on the activity of STING when 'if a sample does not have defective STING activity' for facilitating treating cancer with a desired effect and without undue experimentation.

Without a shared special technical feature, the inventions lack unity with one another.

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

Continuation of item 4: Claims 15-19 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.

Note:

I) Claim 1 is objected as lacking a definition for the first appeared abbreviation "STING" limitation in claims. For the purposes of this ISR, "STING" in claim 1 is rewritten as "stimulator of interferon genes (STING)", based on the Specification (Specification: para [0008] - 'STING (stimulator of interferon genes)').

II) Claim 7 is objected as lacking a definition for the first appeared abbreviation "cGAS" limitation in claims. For the purposes of this ISR, "cGAS" in claim 7 is rewritten as "cyclic GMP-AMP synthase (cGAS)", based on the Specification (Specification: [0008] - 'cGAS (cyclic GMP-AMP synthase,').

III) Claim 18 is objected to as it is self-referring. For the purposes of this ISR, it is assumed that claim 18 depends from claim 17.