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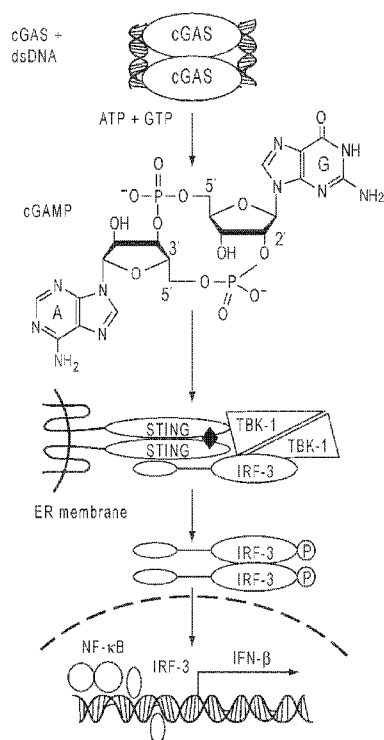
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[Continued on next page]

(54) **Title:** METHOD OF TREATING CANCER WITH CGAMP OR CGASMP

Figure 1



(57) **Abstract:** In one embodiment, a method of treating cancer in a patient comprises administering cGAMP or cGAsMP to a patient having cancer and allowing the cGAMP or cGAsMP to treat the cancer. In another embodiment, a method for enzymatically synthesizing and purifying cGAMP or cGAsMP comprises providing cGAS; combining cGAS with ATP or ATP phosphorothioate, respectively, and GTP to produce cGAMP or cGAsMP; separating cGAMP or cGAsMP from the cGAS and DNA by ultrafiltration; and purifying cGAMP or cGAsMP using ion exchange chromatography and optionally gel filtration chromatography.



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).

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18 August 2016

Declarations under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/65678

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/7084 (2016.01)

CPC - A61K 31/7084

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 31/708, 31/7076, 31/7084; A61P 35/00 (2016.01)

CPC: A61K 47/00, 47/481, 47/48023; C07F 9/65746

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)

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); EBSCO Discovery; IP.com; Google; Google Scholar; Google Patents

KEYWORDS: treat, cancer, administer, cgamp, cGAsMP sting, cgas, level

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	CN 103908468 A (FUDAN UNIVERSITY) July 09, 2014; abstract; paragraphs [0005], [0007], [0017], [0021], [0022]	1-2 --- 3-7
X ---- Y	(LI, X et al.) Cyclic GMP-AMP Synthase Is Activated by Double-Stranded DNA-Induced Oligomerization. Immunity. December 12, 2013. Vol. 39. pp 1019-1031; figure 1; page 1019, column 2, paragraph 1; page 1020, column 1 paragraph 1 to column 2, paragraph 1. dx.doi.org/10.1016/j.immuni.2013.10.019	8 --- 4
Y	US 2013/0039933 A1 (BARBER, GN) February 14, 2013; paragraphs [0113], [0114], [0373], [0520]	3, 5-6
Y	WO 2014/179335 A1 (MEMORIAL SLOAN KETTERING CANCER CENTER) November 06, 2014; paragraphs [0004], [0207]	7

☐ 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

02 March 2016 (02.03.2016)

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/65678

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:

---Please See Supplemental Page---

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.:
1-8

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
Information on patent family members

International application No.
PCT/US15/65678

-Continued from Box No. III Observations where unity of invention is lacking-

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 1-8 are directed toward a method of inhibiting growth of cancer cells and treating cancer in a patient comprising administering cGAMP to a patient; as well as a method of enzymatically synthesizing cGAMP.

Group II, Claims 9-20 are directed toward a method for enzymatically synthesizing cGAsMP, and purifying cGAsMP.

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 treating cancer, not present in Group II; the special technical features of Group II include cGAsMP, not present in Group I.

Groups I and II share the technical features including: a method for enzymatically synthesizing a cyclic G/A dinucleotide comprising: a. providing recombinant cGAS; and b. combining cGAS with ATP or ATP phosphorothioate, GTP, and dsDNA to synthesize the cyclic G/A dinucleotide.

However, these shared technical features are previously disclosed by the article 'Cyclic GMP-AMP Synthase Is Activated by Double-Stranded DNA-Induced Oligomerization' by Li et al. (hereinafter 'Li').

Li discloses a method for enzymatically synthesizing a cyclic G/A dinucleotide (a method for enzymatically synthesizing 2',5' cGAMP (a cyclic G/A dinucleotide); Figure 1; page 1020, column 1) comprising: a. providing recombinant cGAS (providing recombinant cGAS; page 1020, column 1); and b. combining cGAS with ATP, GTP, and dsDNA (combining cGAS with ATP, GTP, and dsDNA; page 1020, column 1) to synthesize the cyclic G/A dinucleotide (to synthesize the 2',5' cGAMP (cyclic G/A dinucleotide); Figure 1; page 1020, column 1).

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 Li reference, unity of invention is lacking.