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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 December 2014 (24.12.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/205199 A3

(51) International Patent Classification:
A01N 43/04 (2006.01) *A61K 39/395* (2006.01)
A01N 43/90 (2006.01)

(21) International Application Number:
PCT/US2014/043155

(22) International Filing Date:
19 June 2014 (19.06.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/838,252	22 June 2013 (22.06.2013)	US
61/887,625	7 October 2013 (07.10.2013)	US
61/934,094	31 January 2014 (31.01.2014)	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, 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.

(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, 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).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

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

(88) Date of publication of the international search report:
18 June 2015

(54) Title: COMPOSITIONS AND METHODS FOR POTENTIATING IMMUNE RESPONSE, ENHANCING IMMUNOTHERAPY, AND INCREASING VACCINE POTENCY

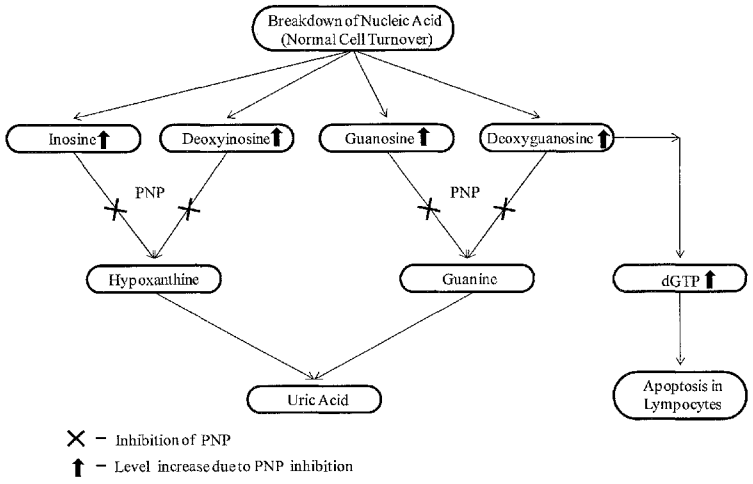

Fig. 1

(57) Abstract: Compositions including at least one PNP inhibitor or at least one PNP inhibitor in combination with one or more agents identified as endogenous adjuvants useful for enhancing the potency of vaccine and cancer immunotherapies being administered for the prevention or treatment of infectious diseases or cancer. The compositions may be formulated as pharmaceutical dosage forms and components may be assembled as kits. Methods for increasing the levels of endogenous adjuvants to enhance the immunogenicity of an antigen as well as to augment the potency of vaccine and cancer immunotherapies are also disclosed.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/04, 43/90; A61K 39/395 (2014.01)
CPC - A61K 31/70; C07D 487/04
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)
CPC: A61K 31/70; C07D 487/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC: A61K 31/70; C07D 487/04; A61K 2039/505 (text search)
USPC: 514/43, 45, 262.1, 265.1; 424/141.1, 158.1 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases: PatBase; Google Scholar; Google Patents
Search terms: purine nucleoside phosphorylase (PNP) inhibitor (e.g. forodesine, Immucillin-H, ulodesine, BCX-4028), vaccine, immunotherapy, adjuvant, endogenous adjuvant (e.g. inosine, guanosine), checkpoint modulator (e.g. anti-PD1), TLR7 agonist, immunos

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0082863 A1 (SIGNORELLI et al.) 12 April 2007 (12.04.2007). Especially para [0017], [0029], [0045], [0074].	1-15
Y	US 6,656,915 B1 (Bantia et al.) 2 December 2003 (02.12.2003). Especially col 1 ln 53-55.	1-15
Y	US 2012/0114649 A1 (Langermann et al.) 10 May 2012 (10.05.2012). Especially para [0027], [0035].	2, 3, 7
Y	US 2005/0054590 A1 (AVERETT). 10 March 2005 (10.03.2005). Especially para [0016].	4
Y	BANTIA et al. Potent orally bioavailable purine nucleoside phosphorylase inhibitor BCX-4208 induces apoptosis in B- and T-lymphocytes--a novel treatment approach for autoimmune diseases, organ transplantation and hematologic malignancies. Int Immunopharmacol July 2010 Vol 10 No 7 Pages 784-790. Especially pg 784 col 2 para 1, pg 785 fig 2, pg 789 col 1 para 3	8-12
Y	KICSKA et al. Immucillin H, a powerful transition-state analog inhibitor of purine nucleoside phosphorylase, selectively inhibits human T lymphocytes. Proc Nat Acad Sci 10 April 2001 Vol 98 No 8 Pages 4593-4598. Especially pg 4594 fig 1.	12
A	Walker et al. "Purine nucleoside phosphorylase deficiency: a mutation update" Nucleosides Nucleotides Nucleic Acids, December 2011, Vol 30 No 12 Pages 1243-1247, abstract	1

☐ 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
05 January 2015 (05.01.2015)	31 MAR 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

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/43155

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:
-----go to Extra Sheet for continuation-------

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.:
Claims 1-15

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.
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Continuation of 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 1-15, drawn to a method for enhancing the potency of a vaccine or an immunotherapy administered to a subject as part of a prevention or treatment regimen, the method comprising: administering a pharmaceutically effective amount of a purine nucleoside phosphorylase (PNP) inhibitor to a subject in conjunction with the vaccine or immunotherapy.

Group II: Claims 16-20, drawn to a composition effective for potentiating an immune system response in a subject being treated with vaccine or cancer immunotherapy, the composition comprising at least one PNP inhibitor and at least one agent identified as an endogenous adjuvant.

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:

Special Technical Features:

Group I has the special technical feature of administering a vaccine or immunotherapy, not required by Group II.

Group II has the special technical feature of an endogenous adjuvant, not required by Group I.

Common Technical Feature:

Groups I and II share the common technical feature of an amount of a purine nucleoside phosphorylase (PNP) inhibitor. Group II (composition) can be related to Group I as part of a composition used in the method of Group I.

However, said common technical feature does not represent a contribution over the prior art, and is obvious over US 2007/0082863 A1 to SIGNORELLI et al. (hereinafter "Signorelli"), in view of the publication titled "Purine nucleoside phosphorylase deficiency: a mutation update" by WALKER et al. (hereinafter "Walker") [Nucleosides Nucleotides Nucleic Acids December 2011 Vol 30 No 12 Pages 1243-1247].

Signorelli teaches inosine analogs administered as an adjuvant to enhance a vaccine response (para [0017]; "The present invention provides combining antigens with an inosine-containing compound to be administered in the form of a vaccine thereby enhancing the response to the vaccine antigens wherein, the inosine-containing compound is considered as an adjuvant"). Signorelli does not teach administering a pharmaceutically effective amount of a purine nucleoside phosphorylase (PNP) inhibitor to a subject in conjunction with the vaccine. However, Walker teaches excessive and detectable levels of the metabolites inosine, deoxyinosine, guanosine, and deoxyguanosine in PNP-deficient subjects (abstract; "We report biochemical and genetic data on a cohort of seven patients from six families identified as PNPase deficient. In all patients, inosine, deoxyinosine, guanosine, and deoxyguanosine were elevated in urine"). Since inosine-containing compound enhance the potency of a vaccine, it would have been obvious to an artisan of ordinary skill to have elevated endogenous cellular pools of inosine by administering a pharmaceutically effective amount of a PNP-inhibitor, because Walker teaches increased inosine level in PNPase deficient subject.

As the common technical feature was known in the art at the time of the invention, this cannot be considered a common special technical feature that would otherwise unify the groups. The inventions lack unity with one another.

Therefore, Groups I and II lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.