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- (71) Applicant (for all designated States except US): **THE TRUSTEES OF PRINCETON UNIVERSITY** [US/US];
One Nassau Hall, Princeton, NJ 08544 (US).
- (72) Inventors; and
- (71) Applicants (for US only): **RABINOWITZ, Joshua, D.** [US/US]; No. 2 Greenholm Street, Princeton, NJ 08450 (US). **FAN, Jing** [CN/US]; 334 S Yellowstone Dr., Apt. 4, Madison, WI 53705 (US). **DUCKER, Gregory, S.** [US/US]; 130 Washington St., Apt 5, Rocky Hill, NJ 08553 (US).
- (74) Agents: **AUERBACH, Jeffrey, I.** et al.; AuerbachSchrot LLC, 2200 Research Blvd., Suite 560, Rockville, MD 20850 (US).
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(54) Title: NADPH PRODUCTION BY THE 10-FORMYL-THF PATHWAY, AND ITS USE IN THE DIAGNOSIS AND TREATMENT OF DISEASE

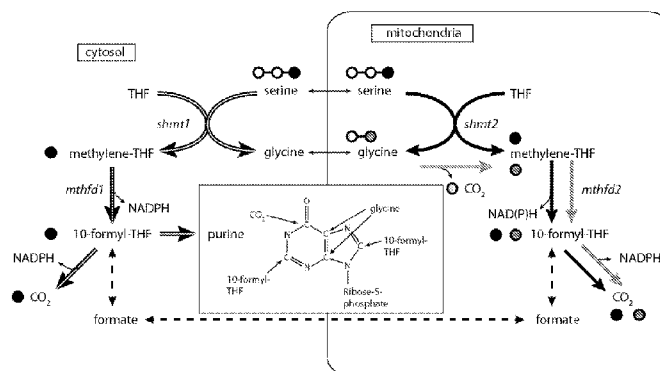


Figure 3A

(57) Abstract: The present invention relates to the recognition of a 10-formyl-THF pathway for producing NADPH, and to the use of that recognition in the diagnosis and treatment of cancer and metabolic disease, and in the development of new antineoplastic agents and/or regimens, and new therapeutics for treating metabolic disease.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2015/021578

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - G01N 33/50 (2015.01) CPC - G01N 33/5008 (2015.09) 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) - C12Q 1/68; G01N 33/15, 33/48, 33/50 (2015.01) CPC - G01N 33/5008, 33/5014, 33/5038, 33/5088 (2015.09)		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched CPC - G01N 33/5008, 33/5014, 33/5038, 33/5088 (2015.09) (keyword delimited) US Classes - 530/356, 357; 536/23.1, 23.5		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatBase, Google Patents, Google, PubMed Search terms used: thymine, serine, 2H, deuterium, isotope, label, tag, biomolecule, folate inhibition, mitochondria, cytosolic, cancer		
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 2013/0273533 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA et al) 17 October 2013 (17.10.2013) entire document	1-4, 6 ----- 5, 9-12
X	US 2007/0249545 A1 (RODRIGUEZ-LOPEZ et al) 25 October 2007 (25.10.2007) entire document	18, 19
Y	BIRRELL et al. "Investigation of NADH Binding, Hydride Transfer, and NAD ⁺ Dissociation during NADH Oxidation by Mitochondrial Complex I Using Modified Nicotinamide Nucleotides," Biochemistry, 17 May 2013 (17.05.2013), Vol. 52, Pgs. 4048-4055. entire document	5
Y	ANGUERA et al. "Regulation of Folate-mediated One-carbon Metabolism by 10-Formyltetrahydrofolate Dehydrogenase," The Journal of Biological Chemistry, 07 July 2006 (07.07.2006), Vol. 281, No. 27, Pgs. 18335-18342. entire document	9-12
P, X	FAN et al. "Quantitative flux analysis reveals folate-dependent NADPH production," Nature, 12 June 2014 (12.06.2014), Vol. 510, Iss. 7504, Pgs. 298-302. entire document	1-6, 9-12, 18, 19
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>		
Date of the actual completion of the international search 18 September 2015		Date of mailing of the international search report 16 OCT 2015
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Authorized officer Blaine Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2015/021578

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.: 7, 8, 13-17, 20
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:

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.