UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 13/939,519 | 07/11/2013 | Leonard Luan C. Dang | C2081-701320 | 2110 |

94970 7590 09/07/2017

LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

| EXAMINER | |
|---|---|
| HIXSON, CHRISTOPHER | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1797 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 09/07/2017 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DOCKETING@LALaw.COM
pair_agios@firsttofile.com
CKent@LALaw.com

| Notice of Abandonment | Application No. | Applicant(s) |
|---|---|---|
| | 13/939,519 | Dang et al. |
| | Examiner | Art Unit |
| | CHRISTOPHER A HIXSON | 1797 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--*

This application is abandoned in view of:

1. ☑ Applicant's failure to timely file a proper reply to the Office letter mailed on 09 February 2017.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 to the final rejection. (A proper reply under 37 CFR 1.113 to a final rejection consists only of:(1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) if this is utility or plant application, a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. Note that RCEs are not permitted in design applications.)
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☑ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $ _____ is insufficient. A balance of $ _____ is due.
   The issue fee required by 37 CFR 1.18 is $ _____ . The publication fee, if required by 37 CFR 1.18(d), is $ _____ .
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record or other party authorized under 37 CFR 1.33 (b). See 37 CFR 1.138(b).

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

_____

| /Christopher Adam Hixson/<br>Primary Examiner, Art Unit 1797 | |
|---|---|

Petitions to revive under 37 CFR 1.137, or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 13/939,519 | 07/11/2013 | Leonard Luan C. Dang | C2081-701320 | 2110 |

94970 7590 05/02/2017

LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

| EXAMINER |
|---|
| HIXSON, CHRISTOPHER |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1797 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 05/02/2017 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DOCKETING@LALaw.COM
pair_agios@firsttofile.com
CKent@LALaw.com

| Applicant-Initiated Interview Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 13/939,519 | DANG ET AL. | |
| | Examiner | Art Unit | |
| | Christopher A. Hixson | 1797 | |

All participants (applicant, applicant's representative, PTO personnel):

(1) *Christopher A. Hixson*. (3)_____.

(2) *Asimina T. Georges Evangelinos*. (4)_____.

Date of Interview: *26 April 2017*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☒101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

*Previously, the examiner had offered certain subject matter to the applicants as potentially allowable subject matter. At the time, the declined the examiner's offer. However, at last RCE filing, they amended their claims to comport with the examiner's previous offer. The applicant phoned today to inquire as to why instead of a notice of allowance, the non-final rejection mailed 9 Feburary 2017 was issued. The examiner explained that in the time since the original offer was made, he realized (after training and discussion with collegues) that the subject matter previously identified as allowable was in fact not subject matter eligible. The examiner indicated that subject matter he had previously considered non-conventional could in fact be demonstrated as being conventional, and in his rejection he cited evidence supporting this understanding. The applicant informed the examiner that though the evidence was received by them, it was illegible. The examiner agreed to provide the best copy he could obtain .*

**Applicant recordation instructions:** The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

**Examiner recordation instructions**: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

| /Christopher A. Hixson/<br>Primary Examiner, Art Unit 1797 | |
|---|---|

# Summary of Record of Interview Requirements

**Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record**
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

**Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews**
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

---

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

**Examiner to Check for Accuracy**

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 13/939,519 | 07/11/2013 | Leonard Luan C. Dang | C2081-701320 | 2110 |

94970 7590 02/09/2017

LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

| EXAMINER | |
|---|---|
| HIXSON, CHRISTOPHER | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1797 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 02/09/2017 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DOCKETING@LALaw.COM
pair_agios@firsttofile.com
CKent@LALaw.com

| Office Action Summary | Application No. 13/939,519 | Applicant(s) DANG ET AL. | |
|---|---|---|---|
| | Examiner Christopher A. Hixson | Art Unit 1797 | AIA (First Inventor to File) Status No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 January 2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5)☒ Claim(s) *93-95,99,101-103 and 105-107* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *93-95,99,101-103 and 105-107* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

1. The present application is being examined under the pre-AIA first to invent provisions.

## DETAILED ACTION

2. The RCE dated 13 January 2017 is acknowledged. Claims 1-92, 96-98, 100, 104, 108 are cancelled. Therefore claims 93-95, 99, 101-103, 105-107 are pending and considered on the merits below.

3. The rejection over enablement is withdrawn. Other rejections over 35 USC 101 are maintained, as the amendment merely changes the precise grounds upon which the claims can be rejected. A new rejection over indefiniteness is presented.

### *Continued Examination Under 37 CFR 1.114*

4. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 13 January 2017 has been entered.

### *Priority*

5. Because no support for the correlation between mutants of IDH1 and IDH2 and 2HG neoactivity, required by all claims as filed, can be found in earlier priority documents, priority for claims including such a requirement are traced to US 61/173,518, filed 28 April 2009.

### *Claim Interpretation*

6. The examiner notes that the word "neoactivity" is defined by the applicant's specification. Provisional application 61/160,253 is incorporated by reference into the present disclosure in [0001]. On p.3 of the '253 application, neoactivity is said to mean an activity which arises as a result of a mutation of an enzyme. In [0018] of the present specification, 2HG neoactivity is defined to "refer[] to the ability to convert alpha ketoglutarate to 2-hydroxyglutarate (sometimes referred to herein as 2HG)" because of the mutation of an enzyme.

### *Claim Rejections - 35 USC § 112*

7. The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. **Claim(s) 93-95 and 99, 101-103, and 105-107** is/are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Regarding claim 93, the claim requires that the MR signal is to be at about 2.5ppm. However, the chemical shift of a MR signal depends entirely on a variety of factors, including the specific nature of the nuclei being probed (proton, $^{13}C$, etc). In the claim, this is not specified. Because this is required to understand what is being claimed, and because the claim is silent as to this issue, the claim lacks the required clarity, and is therefore rejected.

Dependent claims suffer from a similar defect, and are rejected on the same basis.

### *Claim Rejections - 35 USC § 101*

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

**Claims 93-95 and 99, 101-103, and 105-107** are rejected under 35 U.S.C. 101 because the claimed invention is directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more.

Claim(s) 93-95 and 99, 101-103, and 105-107 is/are directed to a method which recites both an abstract idea and a natural law. Claim 93 is directed to the correlation of 2HG presence, distribution, or level in a particular type of subject and the “presence or

susceptibility to cancer" in a step in which the patient is said be “evaluated” (the correlation is a natural law, the implied diagnosis is an abstract idea).

The claim(s) does/do not include additional elements that are sufficient to amount to significantly more than the judicial exception.

Regarding claim 93, the analysis step is recited features which are understood by the examiner to be conventional, and because it is a necessary step to gather information for the abstract idea and is otherwise necessary to make much use of the natural correlation, it cannot be said to add anything significantly more to the claim. Specifically, one is to measure the level "non-invasively by imaging or spectroscopic analysis with a signal at about 2.5 ppm." In a previous action, the examiner officially noted that MRI has been used to detect particular molecules in a subject (see the molecular MRI field), but this went unchallenged and so is taken as admitted. Additionally, the examiner cited to Sosnovik et al. (Curr Op Biotech 2007), pp.7-8, and this was further evidence that such is to be considered conventional by the examiner.

Furthermore, as is described by McRobbie et al. (MRI from Picture to Proton 2007) describes that glutamine and glutamate-type analytes are generally found by looking at chemical shifts at around 2.5 ppm (p.308, first column, first few lines).

Even looking to the claim as a whole, the examiner sees nothing "significantly more" capable of conveying subject matter eligibility.

Dependent claims fail to add anything significantly more, and many simply raise new issues of subject matter eligibility.

Claims such as 94, 95, 101-103, and 105-107 simply appear to refine the natural law and/or the abstract idea claimed and therefore cannot be said to add something "significantly more."

Claims such as claims 99 and 104 for example recite particulars of the analysis step, but do so in ways which remain entirely conventional. In a previous action, the examiner officially noted that MRI has been used to detect particular molecules in a subject (see the molecular MRI field), but this went unchallenged and so is taken as admitted. Additionally, the examiner cited to Sosnovik et al. (Curr Op Biotech 2007), pp.7-8, and this was further evidence that such is to be considered conventional by the examiner. That one must analyze "a tissue, product, or bodily fluid of the subject" scarcely limits the analysis step in any meaningful way. The examiner does not see that these limitations add something significantly more as is required when taken individually or when considering the claim as a whole.

***Response to Arguments***

10. Applicant's arguments filed 15 September 2016 have been fully considered but they are not persuasive.

The applicants appear to argue on the basis of their amendment. However, evidence to reject the present claims is presented above.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher A. Hixson whose telephone number is (571)270-5027. The examiner can normally be reached on M-F 9 am - 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lyle Alexander can be reached on (571)272-1254. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christopher A. Hixson/
Primary Examiner, Art Unit 1797

| Notice of References Cited | Application/Control No. 13/939,519 | Applicant(s)/Patent Under Reexamination DANG ET AL. | |
|---|---|---|---|
| | Examiner Christopher A. Hixson | Art Unit 1797 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | CPC Classification | US Classification |
|---|---|---|---|---|---|---|
| | A | US- | | | | |
| | B | US- | | | | |
| | C | US- | | | | |
| | D | US- | | | | |
| | E | US- | | | | |
| | F | US- | | | | |
| | G | US- | | | | |
| | H | US- | | | | |
| | I | US- | | | | |
| | J | US- | | | | |
| | K | US- | | | | |
| | L | US- | | | | |
| | M | US- | | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | CPC Classification |
|---|---|---|---|---|---|---|
| | N | | | | | |
| | O | | | | | |
| | P | | | | | |
| | Q | | | | | |
| | R | | | | | |
| | S | | | | | |
| | T | | | | | |

**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | McRobbie, Donald W. et al. "MRI from Picture to Proton." Cambridge Univ. Press (2007). pp.307-308. |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | Examiner | Art Unit |
| | CHRISTOPHER A HIXSON | 1797 |

| CPC- SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| A61B5/055 | 6 feb 2017 | cah |
| A61K31/41,426 | 6 feb 2017 | cah |
| A61K45/06 | 6 feb 2017 | cah |
| A61K2300/00 | 6 feb 2017 | cah |
| C12N15/1137 | 6 feb 2017 | cah |
| C12N2310/14 | 6 feb 2017 | cah |
| C12Q1/32,6886 | 6 feb 2017 | cah |
| C12Y101/01042 | 6 feb 2017 | cah |
| G01N33/574 | 6 feb 2017 | cah |
| G06F19/328 | 6 feb 2017 | cah |

| CPC COMBINATION SETS - SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| US CLASSIFICATION SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

| SEARCH NOTES | | |
|---|---|---|
| Search Notes | Date | Examiner |
| searched in east as attached, inventor name search, google.com, scholar.google.com | 4 sept 2015 | cah |
| searched in east as attached, inventor name search, google.com, scholar.google.com | 26 may 2016 | cah |
| search in google as attached, inventor name search | 7 oct 2016 | cah |
| searched in east as attached, inventor name search | 6 feb 2017 | cah |

| INTERFERENCE SEARCH | |
|---|---|
| | |

| US Class/ CPC Symbol | US Subclass / CPC Group | Date | Examiner |
|---|---|---|---|
| | | | |

| | |
|---|---|
| | |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | **Examiner** | **Art Unit** |
| | CHRISTOPHER A HIXSON | 1797 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/04/2015 | 06/02/2016 | 10/07/2016 | 02/06/2017 | | | | | |
| | 1 | - | - | - | - | | | | | |
| | 2 | - | - | - | - | | | | | |
| | 3 | - | - | - | - | | | | | |
| | 4 | - | - | - | - | | | | | |
| | 5 | - | - | - | - | | | | | |
| | 6 | - | - | - | - | | | | | |
| | 7 | - | - | - | - | | | | | |
| | 8 | - | - | - | - | | | | | |
| | 9 | - | - | - | - | | | | | |
| | 10 | - | - | - | - | | | | | |
| | 11 | - | - | - | - | | | | | |
| | 12 | - | - | - | - | | | | | |
| | 13 | - | - | - | - | | | | | |
| | 14 | - | - | - | - | | | | | |
| | 15 | - | - | - | - | | | | | |
| | 16 | - | - | - | - | | | | | |
| | 17 | - | - | - | - | | | | | |
| | 18 | - | - | - | - | | | | | |
| | 19 | - | - | - | - | | | | | |
| | 20 | - | - | - | - | | | | | |
| | 21 | - | - | - | - | | | | | |
| | 22 | - | - | - | - | | | | | |
| | 23 | - | - | - | - | | | | | |
| | 24 | - | - | - | - | | | | | |
| | 25 | - | - | - | - | | | | | |
| | 26 | - | - | - | - | | | | | |
| | 27 | - | - | - | - | | | | | |
| | 28 | - | - | - | - | | | | | |
| | 29 | - | - | - | - | | | | | |
| | 30 | - | - | - | - | | | | | |
| | 31 | - | - | - | - | | | | | |
| | 32 | - | - | - | - | | | | | |
| | 33 | - | - | - | - | | | | | |
| | 34 | - | - | - | - | | | | | |
| | 35 | - | - | - | - | | | | | |
| | 36 | - | - | - | - | | | | | |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | **Examiner** | **Art Unit** |
| | CHRISTOPHER A HIXSON | 1797 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/04/2015 | 06/02/2016 | 10/07/2016 | 02/06/2017 | | | | | |
| | 37 | - | - | - | - | | | | | |
| | 38 | - | - | - | - | | | | | |
| | 39 | - | - | - | - | | | | | |
| | 40 | - | - | - | - | | | | | |
| | 41 | ✓ | - | - | - | | | | | |
| | 42 | ✓ | - | - | - | | | | | |
| | 43 | ✓ | - | - | - | | | | | |
| | 44 | ✓ | - | - | - | | | | | |
| | 45 | ✓ | - | - | - | | | | | |
| | 46 | ✓ | - | - | - | | | | | |
| | 47 | ✓ | - | - | - | | | | | |
| | 48 | ✓ | - | - | - | | | | | |
| | 49 | ✓ | - | - | - | | | | | |
| | 50 | ✓ | - | - | - | | | | | |
| | 51 | ✓ | - | - | - | | | | | |
| | 52 | ✓ | - | - | - | | | | | |
| | 53 | ✓ | - | - | - | | | | | |
| | 54 | ✓ | - | - | - | | | | | |
| | 55 | ✓ | - | - | - | | | | | |
| | 56 | ✓ | - | - | - | | | | | |
| | 57 | N | - | - | - | | | | | |
| | 58 | N | - | - | - | | | | | |
| | 59 | N | - | - | - | | | | | |
| | 60 | N | - | - | - | | | | | |
| | 61 | N | - | - | - | | | | | |
| | 62 | N | - | - | - | | | | | |
| | 63 | ✓ | - | - | - | | | | | |
| | 64 | ✓ | - | - | - | | | | | |
| | 65 | ✓ | - | - | - | | | | | |
| | 66 | N | - | - | - | | | | | |
| | 67 | N | - | - | - | | | | | |
| | 68 | N | - | - | - | | | | | |
| | 69 | N | - | - | - | | | | | |
| | 70 | N | - | - | - | | | | | |
| | 71 | N | - | - | - | | | | | |
| | 72 | N | - | - | - | | | | | |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | **Examiner** | **Art Unit** |
| | CHRISTOPHER A HIXSON | 1797 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/04/2015 | 06/02/2016 | 10/07/2016 | 02/06/2017 | | | | | |
| | 73 | N | - | - | - | | | | | |
| | 74 | N | - | - | - | | | | | |
| | 75 | N | - | - | - | | | | | |
| | 76 | N | - | - | - | | | | | |
| | 77 | N | - | - | - | | | | | |
| | 78 | N | - | - | - | | | | | |
| | 79 | N | - | - | - | | | | | |
| | 80 | ✓ | - | - | - | | | | | |
| | 81 | ✓ | - | - | - | | | | | |
| | 82 | ✓ | - | - | - | | | | | |
| | 83 | ✓ | - | - | - | | | | | |
| | 84 | ✓ | - | - | - | | | | | |
| | 85 | ✓ | - | - | - | | | | | |
| | 86 | ✓ | - | - | - | | | | | |
| | 87 | ✓ | - | - | - | | | | | |
| | 88 | ✓ | - | - | - | | | | | |
| | 89 | ✓ | - | - | - | | | | | |
| | 90 | ✓ | - | - | - | | | | | |
| | 91 | ✓ | - | - | - | | | | | |
| | 92 | ✓ | - | - | - | | | | | |
| | 93 | ✓ | ✓ | ✓ | ✓ | | | | | |
| | 94 | ✓ | ✓ | ✓ | ✓ | | | | | |
| | 95 | ✓ | ✓ | ✓ | ✓ | | | | | |
| | 96 | ✓ | - | - | - | | | | | |
| | 97 | ✓ | ✓ | - | - | | | | | |
| | 98 | ✓ | ✓ | ✓ | - | | | | | |
| | 99 | ✓ | ✓ | ✓ | ✓ | | | | | |
| | 100 | | ✓ | ✓ | - | | | | | |
| | 101 | | ✓ | ✓ | ✓ | | | | | |
| | 102 | | ✓ | ✓ | ✓ | | | | | |
| | 103 | | ✓ | ✓ | ✓ | | | | | |
| | 104 | | ✓ | ✓ | - | | | | | |
| | 105 | | ✓ | ✓ | ✓ | | | | | |
| | 106 | | ✓ | ✓ | ✓ | | | | | |
| | 107 | | | | ✓ | | | | | |
| | 108 | | | | - | | | | | |

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C. Dang |
| Art Unit | 1797 |
| Examiner Name | C. Hixson |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | | | | | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | | | | | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | | | | | | | |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|

EFS Web 2.1.17

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C. Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 1 | Extended European Search Report for European application no. 16152308.9 dated July 18, 2016 | |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | /Christopher Adam Hixson/ | Date Considered | 02/06/2017 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Lenny Dang |
| Art Unit | 1797 |
| Examiner Name | C. Hixson |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 5021421 | | 1991-06-04 | Hino et al. | |
| | 2 | 5807876 | | 1998-09-15 | Armistead et al. | |
| | 3 | 5965569 | | 1999-10-12 | Camps Garcia et al. | |
| | 4 | 6262113 | | 2001-07-17 | Widdowson et al. | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 20020188027 | A1 | 2002-12-12 | Robinson et al. | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Lenny Dang |
| Art Unit | 1797 |
| Examiner Name | C. Hixson |
| Attorney Docket Number | C2081-701320 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 101296909 | CN | A | 2008-10-29 | Serono Lab | | X |
| | 2 | 0022958 | EP | A1 | 1981-01-28 | Bayer Ag | | ☐ |
| | 3 | 1996030343 | WO | A1 | 1996-10-03 | Merck & Co., Inc | | ☐ |
| | 4 | 1997044322 | WO | A1 | 1997-11-27 | Chiroscience Ltd | | ☐ |
| | 5 | 2001019788 | WO | A2 | 2001-03-22 | Cor Therapeutics, Inc | | ☐ |
| | 6 | 2001019798 | WO | A2 | 2001-03-22 | Cor Therapeutics Inc | | ☐ |
| | 7 | 2001064642 | WO | A2 | 2001-09-07 | Cor Therapeutics, Inc | | ☐ |
| | 8 | 2001064643 | WO | A2 | 2001-09-07 | Cor Therapeutics, Inc | | ☐ |
| | 9 | 2002100822 | WO | A1 | 2002-12-19 | Biovitrum Ab | | ☐ |
| | 10 | 2004089470 | WO | A2 | 2004-10-21 | Novo Nordisk As | | ☐ |
| | 11 | 2005120474 | WO | A2 | 2005-12-22 | Leuven K U Res & Dev | | ☐ |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Lenny Dang |
| Art Unit | 1797 |
| Examiner Name | C. Hixson |
| Attorney Docket Number | C2081-701320 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 12 | 2006034341 | WO | A2 | 2006-03-30 | Xenon Pharmaceuticals Inc | | ☐ |
| | 13 | 2007003934 | WO | A2 | 2007-01-11 | Sterix Ltd | | ☐ |
| | 14 | 2008052190 | WO | A2 | 2008-05-02 | Flynn, Gary et al. | | ☐ |
| | 15 | 2008073670 | WO | A2 | 2008-06-19 | Millennium Pharmaceuticals, Inc | | ☐ |
| | 16 | 2009126863 | WO | A2 | 2009-10-15 | Genentech, Inc | | ☐ |
| | 17 | 2010/129596 | WO | A1 | 2010-11-11 | Agios Pharmaceuticals, Inc | | ☐ |
| | 18 | 2010130638 | WO | A1 | 2010-11-18 | Evotec Ag | | ☐ |
| | 19 | 2011032169 | WO | A2 | 2011-03-17 | Phusis Therapeutics Inc | | ☐ |
| | 20 | 2011047432 | WO | A1 | 2011-04-28 | Fibrotech Therapeutics Pty Ltd | | ☐ |
| | 21 | 2012/092442 | WO | A1 | 2012-07-05 | Agios Pharmaceuticals, Inc | | ☐ |
| | 22 | 2012151452 | WO | A1 | 2012-11-08 | Agios Pharmaceuticals, Inc | | ☐ |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Lenny Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 23 | 97/28128 | WO | A1 | 1997-08-07 | Zeneca Ltd | | ☐ |
| | 24 | 9932463 | WO | A1 | 1999-07-01 | Bayer Ag | | ☐ |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T5 |
|---|---|---|---|
| | 1 | International Preliminary Report for related application No. PCT/US2011/067752 dated April 11, 2013 | |
| | 2 | International Search Report dated March 5, 2012 for related international application no. PCT/US2011/067752. | |
| | 3 | REGISTRY (STN) [online], 2006.08.23 [Retrieved on 2016.01.29] CAS Registration No. 903862-76-0 | |
| | 4 | REGISTRY (STN) [online], 2006.08.23 [Retrieved on 2016.01.29] CAS Registration No. 903869-26-1 | |
| | 5 | REGISTRY (STN) [online], 2007.04.13 [Retrieved on 2016.01.29] CAS Registration No. 929819-92-1 | |
| | 6 | REGISTRY (STN) [online], 2007.04.13 [Retrieved on 2016.01.29] CAS Registration No. 929971-43-7 | |
| | 7 | REGISTRY (STN) [online], 2009.04.19 [Retrieved on 2016.01.29] CAS Registration No. 1136498-70-8 | |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Lenny Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 8 | REGISTRY (STN) [online], 2009.08.27 [Retrieved on 2016.01.29] CAS Registration No. 1176756-98-1 | |
| | 9 | STN Tokyo, Registry Number 1001833-18-6, Entered STN on February 6, 2008, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [(4-methyl-l-piperazinyl)carbonyl]phenyl]–" | |
| | 10 | STN Tokyo, Registry Number 1030142-35-8, Entered STN on June 24, 2008, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-[(5-methyl-3-isoxazolyl)methyl]-l-piperazinyl]carbonyl]phenyl]-" | |
| | 11 | STN Tokyo, Registry Number 1031531-78-8, Entered STN on June 29, 2008 Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, N-4[4-[(4-acetyl-1-piperazinyl)carbonyl]phenyl]-2,3-dihydro-" | |
| | 12 | STN Tokyo, Registry Number 1057928-35-4, Entered STN on October 7, 2008, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(2-pyridinyl)-l-piperazinyl]carbonyl]phenyl]-" | |
| | 13 | STN Tokyo, Registry Number 1240875-006, entered STN on September 14, 2010, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4-[[4-(2-thiazolyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 14 | STN Tokyo, Registry Number 748791-86-8, Entered STN on September 21, 2004, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, N-[4- [[4-(2-furanylcarbonyl)-1-piperazinyl]carbonyl]phenyl]-2,3-dihydro-" | |
| | 15 | STN Tokyo, Registry Number 878469-24-0, Entered STN on March 29, 2006, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4-[[4-(2-pyrimidinyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 16 | STN Tokyo, Registry Number 878474-39-6, Entered STN on March 29, 2006, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4[(4-phenyl-1-piperazinyl)carbonyl]phenyl]-" | |
| | 17 | STN Tokyo, Registry Number 878590-33-1, Entered STN on March 30, 2006, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4-{[4-(tetrahydro-2-furanyl)methyl]-1-piperazinyl]carbonyl]phenyl]-" | |
| | 18 | STN Tokyo, Registry Number 878943-66-9 Entered STN on April 2, 2006, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 3,4-dihydro-N-[[4-(2-pyrimidinyl)-1-piperazinyl)carbonyl]phenyl]-" | |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Lenny Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 19 | STN Tokyo, Registry Number 878956-06-0, Entered STN on April 2, 2006, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, N-[4- [[4-(cyclopropylcarbonyl)-1-piperazinyl]carbonyl]phenyl]-2,3-dihydro-" | |
| | 20 | STN Tokyo, Registry Number 9200679-46-5, Entered STN on February 13, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(4-pyridinyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 21 | STN Tokyo, Registry Number 920822-52-2, Entered STN on February 14, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, N-[4- [[4-(4-fluoropheyl)-1-piperazinyl]carbonyl]phenyl] - 2,3dihydro-" | |
| | 22 | STN Tokyo, Registry Number 920824-56-2, Entered STN on February 14, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(3-thienylmethyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 23 | STN Tokyo, Registry Number 920847-34-3, Entered STN on February 14, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(2-methylphenyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 24 | STN Tokyo, Registry Number 920875-39-4, Entered STN on February 14, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(2-hydroxyphenyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 25 | STN Tokyo, Registry Number 920902-88-1, Entered STN on February 14, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(2-thienylmethyl)-l-piperazinyl]carbonyl]phenyl]-" | |
| | 26 | STN Tokyo, Registry Number 920921-09-1 Entered STN on February 14, 2007, Chemical Abstracts Index Name "2H-1, 5-Benzodioxepin-7-sulfonamide, 3,4-dihydro-N-[4-[[4-(2pyridinyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 27 | STN Tokyo, Registry Number 920924-42-1, Entered STN on February 14, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(2-pyridinylmethyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 28 | STN Tokyo, Registry Number 941220-77-5, Entered STN on July 4, 2007, Chemical Abstracts Index Name "2H-1, 5-Benzodioxepin-7-sulfonamide, 3,4-dihydro-N-[4-[(4-methyl-l-piperazinyl)carbonyl]phenyl]-" | |
| | 29 | Lutker et al, "Crystal Polymorphism in a Carbamazepine Derivative: Oxcarbazepine". NIH Public Access. J Pharm Sci. 2010 February ; 99(2): 794-803. doi: 10.1002/jps.21873 | |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Lenny Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | |
|---|---|---|
| | 30 | Rao et al., "Polymorphism in Drugs and its Significance in Therapeutics". Journal of Scientific & Industrial Research Vol. 46 October 1987 pp 450-455. |
| | 31 | Docoslis et al., "Characterization of the Distribution, Polymorphism, and Stability of Nimodipine in Its Solid Dispersions in Polyethylene Glycol by Micro-Raman Spectroscopy and Powder X-Ray Diffraction". The AAPS Journal 2007; 9 (3) Article 43, E361-E370. |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | /Christopher Adam Hixson/ | Date Considered | 02/06/2017 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

**EAST Search History**

**EAST Search History (Prior Art)**

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| L1 | 229053 | @pd>="20160526" | USPAT | OR | OFF | 2017/02/06 05:38 |
| L2 | 128542 | a61b5/055.cpc. or a61k31/41,426.cpc. or a61k45/06.cpc. or a61k2300/00.cpc. or c12n15/1137.cpc. or c12n2310/14.cpc. or c12q1/32,6886.cpc. or c12y101/01042.cpc. or g01n33/574.cpc. or g06f19/328.cpc. | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 05:38 |
| L3 | 3165 | 1 and L2 | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 05:38 |
| L4 | 2063 | cancer and 3 | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 06:04 |
| L5 | 536590 | (magnetic with resonance) or (MRI or NMR) | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 06:04 |
| L6 | 962 | 4 and 5 | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 06:04 |
| L7 | 6 | (("DANG") near3 ("Leonard")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 06:27 |
| L8 | 56 | (("GROSS") near3 ("Stefan")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 06:27 |
| L9 | 864 | (("JANG") near3 ("Hyun")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 06:27 |
| L10 | 18 | (("JIN") near3 ("Shengfang")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 06:27 |
| L11 | 35 | (("SU") near3 ("Shin-San")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 06:27 |
| L12 | 271 | (("THOMPSON") near3 ("Craig")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 06:27 |
| L13 | 1220 | L7 or L8 or L9 or L10 or L11 or L12 | US- | OR | OFF | 2017/02/06 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | PGPUB; USPAT; USOCR | | | 06:27 |
| L14 | 54 | 1 and 13 | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 06:27 |
| L15 | 7 | cancer and 14 | US-PGPUB; USPAT; USOCR | OR | OFF | 2017/02/06 06:28 |
| L16 | 5 | ("5021421" \| "5807876" \| "5965569" \| "6262113" \| "20020188027").PN. | US-PGPUB; USPAT | OR | OFF | 2017/02/06 06:34 |
| S1 | 1 | "8883438".did. | USPAT | OR | OFF | 2016/05/26 07:56 |
| S2 | 40524 | a61b5/055.cpc. or a61k31/41,426.cpc. or a61k45/06.cpc. or a61k2300/00.cpc. or c12n15/1137.cpc. or c12n2310/14.cpc. or c12q1/32,6886.cpc. or c12y101/01042.cpc. or g01n33/574.cpc. or g06f19/328.cpc. | USPAT | OR | OFF | 2016/05/26 08:02 |
| S3 | 244516 | @pd>="20150904" | USPAT | OR | OFF | 2016/05/26 08:02 |
| S4 | 3065 | S2 and S3 | USPAT | OR | OFF | 2016/05/26 08:02 |
| S5 | 1925 | S4 and cancer | USPAT | OR | OFF | 2016/05/26 08:02 |
| S6 | 0 | S5 and hydroxygluar$4 | USPAT | OR | OFF | 2016/05/26 08:03 |
| S7 | 0 | S5 and hydroxy?gluar$4 | USPAT | OR | OFF | 2016/05/26 08:03 |
| S8 | 130 | S5 and HG | USPAT | OR | OFF | 2016/05/26 08:03 |
| S9 | 117353 | a61b5/055.cpc. or a61k31/41,426.cpc. or a61k45/06.cpc. or a61k2300/00.cpc. or c12n15/1137.cpc. or c12n2310/14.cpc. or c12q1/32,6886.cpc. or c12y101/01042.cpc. or g01n33/574.cpc. or g06f19/328.cpc. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:03 |
| S10 | 527642 | @pd>="20150904" | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:03 |
| S11 | 9087 | S9 and S10 | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:04 |
| S12 | 5579 | S11 and cancer | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:04 |
| S13 | 374 | HG and S12 | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:04 |
| S14 | 6 | (("DANG") near3 ("Leonard")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:08 |

| | | | | | | |
|---|---|---|---|---|---|---|
| S15 | 52 | (("GROSS") near3 ("Stefan")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:09 |
| S16 | 778 | (("JANG") near3 ("Hyun")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:09 |
| S17 | 17 | (("JIN") near3 ("Shengfang")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:09 |
| S18 | 31 | (("SU") near3 ("Shin-San")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:09 |
| S19 | 267 | (("THOMPSON") near3 ("Craig")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:09 |
| S20 | 1 | "14235513" | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/06/02 10:43 |
| S21 | 1 | 13/625275.app. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/06/02 12:41 |
| S22 | 1 | "20110207039".did. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/06/02 13:08 |

**EAST Search History (Interference)**

<This search history is empty>

**2/6/2017 6:52:37 AM**
**C:\Users\chixson\Documents\EAST\Workspaces\13939519-3.wsp**

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


| PATENT APPLICATION FEE DETERMINATION RECORD<br>Substitute for Form PTO-875 | Application or Docket Number<br>13/939,519 | Filing Date<br>07/11/2013 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY**: ☒ LARGE ☐ SMALL ☐ MICRO

## APPLICATION AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | RATE ($) | FEE ($) |
|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | |
| ☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | |

## APPLICATION AS AMENDED – PART II

| AMENDMENT | 01/13/2017 | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|
| | Total (37 CFR 1.16(i)) | * 10 | Minus | ** 20 | = 0 | X $80 = | 0 |
| | Independent (37 CFR 1.16(h)) | * 1 | Minus | ***3 | = 0 | X $420 = | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | |
| | | | | | | TOTAL ADD'L FEE | **0** |

| AMENDMENT | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|
| | Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | |
| | | | | | | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
SUSAN HAY

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

# REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
## (Submitted Only via EFS-Web)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Application Number | 13939519 | Filing Date | 2013-07-11 | Docket Number (if applicable) | C2081-701320 | Art Unit | 1797 |
| First Named Inventor | Leonard Luan C. Dang | | | Examiner Name | C. Hixson | | |

**This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.**
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not comply with the requirements of 35 U.S.C. 371, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV.

### SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

### MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

### FEES

**The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 50/2762

### SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


| Signature of Registered U.S. Patent Practitioner | | | |
|---|---|---|---|
| Signature | /Catherine M. McCarty/ | Date (YYYY-MM-DD) | 2017-01-13 |
| Name | Catherine M. McCarty | Registration Number | 54301 |

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

# Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: January 13, 2017
Electronic Signature for Catherine M. McCarty: /Catherine M. McCarty/

Docket No.: C2081-701320
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Leonard Luan C Dang et al.

Application No.: 13/939,519 | Confirmation No.: 2110

Filed: July 11, 2013 | Art Unit: 1797

For: METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | Examiner: C. Hixson

**AMENDMENT AFTER FINAL ACTION UNDER 37 C.F.R. § 1.116**

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

**INTRODUCTORY COMMENTS**

In response to the Final Office Action dated October 14, 2016, please amend the above-identified U.S. patent application as follows:

**Amendments to the Claims** begin on page 2 of this paper.

**Remarks** begin on page 4 of this paper.

## AMENDMENTS TO THE CLAIMS

*Please replace all previously filed claims for the application with the following listing of claims:*

Listing of the Claims:

1. – 92. (Canceled)

93. (Currently Amended) A method of evaluating a subject for the presence or susceptibility to a cancer having a somatic allele, which encodes a mutant IDH enzyme having a neoactivity, the method comprising analyzing the subject or a sample from the subject for the presence, distribution, or level of 2HG, wherein the presence or level of 2HG by magnetic resonance spectroscopy is indicated by a signal at about 2.5ppm, and wherein the subject does not have or is not diagnosed as having 2-hydroxyglutaric aciduria, thereby evaluating the subject for such cancer.

94. (Previously Presented) The method of claim 93, wherein the cancer is selected from the group consisting of an astrocytic tumor, an oligodendroglial tumor, an oligoastrocytic tumor, an anaplastic astrocytoma, fibrosarcoma, paraganglioma, prostate cancer, acute lymphoblastic leukemia, and acute myelogenous leukemia.

95. (Previously Presented) The method of claim 93, wherein the cancer is a glioblastoma.

96. – 98. (Cancelled)

99. (Previously Presented) The method of claim 93, wherein the presence, distribution or level of 2HG is determined by evaluating a tissue, product or bodily fluid of the subject.

100. (Cancelled)

101. (Currently Amended) The method of claim [[100]]93, wherein the mutant IDH enzyme is IDH1.

102. (Previously Presented) The method of claim 101, wherein the mutant IDH1 enzyme is selected from the group consisting of R132H, R132C, R132S, R132G, R132L, and R132V.

103. (Currently Amended) The method of claim [[100]]93, wherein the mutant IDH enzyme is IDH2.

104. (Cancelled)

105. (Previously Presented) The method of claim 102, wherein the IDH2 mutation is selected from the group consisting of R172K, R172M, R172S, R172G, and R172W.

106. (Previously Presented) The method of claim 93, wherein detecting the presence of 2HG in a subject by magnetic resonance spectroscopy indicates the presence of a cancer in the subject.

107. (Currently Amended) The method of claim [[104]]93, wherein the cancer is a glioma.

108. (Cancelled)

## REMARKS

Claims Status

Claims 93-95 and 98-106 are pending. Due to a clerical error, there are two different claims numbered 102 and two different claims numbered 103. The second occurrence of claim 102 and 103, and claims 104 to 106 were re-numbered as claims 104 to 108. Claims 1-92, 96-98, 100, re-numbered claim 104 and re-numbered claim 108 are cancelled. Claim 101, the first instance of claim 103, and re-numbered claim 107 are amended to depend from claim 93.

Claim 93 is amended to recite that the cancer evaluated for the presence or susceptibility has a somatic allele, which encodes a mutant IDH enzyme having a neoactivity. Claim 93 is further amended to recite that the presence or level of 2HG measured by magnetic resonance spectroscopy is indicated by a signal at about 2.5ppm. Upon entry of this amendment, claims 93-95, 99, 101-103 and 105 to 107 will be pending. No new matter has been added by these amendments.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 93-95, 97-99 and 104-106 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. The Office contends that elevated 2HG does not necessarily correlate with cancer generally. Solely to expedite prosecution of this application, Applicants have amended independent claim 93 to recite that the cancer has a somatic allele, which encodes a mutant IDH enzyme having a neoactivity, which is recited in claim 100, now cancelled, and which was not rejected by the Office. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph, of independent claim 93 and dependent claims 94-95, 97-99 and 104-106 is rendered moot and should be withdrawn.

Rejection under 35 U.S.C. § 101

Claims 93-95 and 97-105 are rejected under 35 U.S.C. § 101 as allegedly being directed to subject matter that is not patent eligible. The Office contends that the claims recite an abstract idea, *i.e.*, a judicial exception, and therefore the claims are not patent eligible. Solely to expedite prosecution of this application, Applicants have amended claim 93 to recite that the presence or level of 2HG measured by magnetic resonance spectroscopy is indicated by a signal at about

2.5ppm, which is recited in claim 106 (re-numbered as claim 108), which is now cancelled, and which was not rejected by the Office. As such, the rejection under 35 U.S.C. § 101 of claim 93 and its dependent claims 94-95 and 97-105 should be withdrawn.

## CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Dated: January 13, 2017

Respectfully submitted,

Electronic signature: /Catherine M. McCarty/
Catherine M. McCarty
Registration No.: 54,301
Asimina T. Georges Evangelinos
Registration No.: 66,888
LANDO & ANASTASI, LLP
Riverfront Office Park
One Main Street, Suite 1100
Cambridge, Massachusetts 02142
(617) 395-7000

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: January 13, 2017
Electronic Signature for Catherine M. McCarty: /Catherine M. McCarty/

Docket No.: C2081-701320

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Leonard Luan C. Dang et al.

Application No.: 13/939,519 | Confirmation No.: 2110

Filed: July 11, 2013 | Art Unit: 1797

For: METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | Examiner: C. Hixson

**INFORMATION DISCLOSURE STATEMENT (IDS)**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement, pursuant to 37 C.F.R. § 1.114(c), accompanies the Request for Continued Examination (37 C.F.R. § 1.114) submitted herewith.

Submitted herewith is a copy of the non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2). The Applicant would like to bring to the Examiner's attention the attached Extended European Search Report for European application no. 16152308.9.

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Applicant believes no fee is due with this response. However, if a fee is due, the Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50/2762, under Order No. C2081-701320.

Dated: January 13, 2017

Respectfully submitted,

Electronic signature: /Catherine M. McCarty/
Catherine M. McCarty
Registration No.: 54,301
Asimina T. Georges Evangelinos
Registration No.: 66,888
LANDO & ANASTASI, LLP
Riverfront Office Park
One Main Street, Suite 1100
Cambridge, Massachusetts 02142
(617) 395-7000

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C. Dang |
| Art Unit | 1797 |
| Examiner Name | C. Hixson |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | | | | | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | | | | | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | | | | | | | |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C. Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 1 | Extended European Search Report for European application no. 16152308.9 dated July 18, 2016 | |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C. Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| Signature | /Catherine M. McCarty/ | Date (YYYY-MM-DD) | 2017-01-13 |
|---|---|---|---|
| Name/Print | Catherine M. McCarty | Registration Number | 54,301 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 13939519 |
| **Filing Date:** | 11-Jul-2013 |
| **Title of Invention:** | METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS |
| **First Named Inventor/Applicant Name:** | Leonard Luan C. Dang |
| **Filer:** | Catherine M. McCarty/Jeannie Le |
| **Attorney Docket Number:** | C2081-701320 |

Filed as Large Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| RCE- 1st Request | 1801 | 1 | 1200 | 1200 |
| | | **Total in USD ($)** | | **1200** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 28058382 |
| **Application Number:** | 13939519 |
| **International Application Number:** | |
| **Confirmation Number:** | 2110 |
| **Title of Invention:** | METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS |
| **First Named Inventor/Applicant Name:** | Leonard Luan C. Dang |
| **Customer Number:** | 94970 |
| **Filer:** | Catherine M. McCarty |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | C2081-701320 |
| **Receipt Date:** | 13-JAN-2017 |
| **Filing Date:** | 11-JUL-2013 |
| **Time Stamp:** | 13:53:45 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Request for Continued Examination (RCE) | Request_for_Continued_Examination_Fillable_PDF.pdf | 1349952<br>abf97c859bc41a35be2d120d1a9fae9ee14f9c4e | no | 3 |

**Warnings:**

| | | | | | |
|---|---|---|---|---|---|
| **Information:** | | | | | |
| 2 | | Response_to_final_rejection_mailed_10_14_2016_FOR_FILING.pdf | 35654<br>d61277094d76595b1de75b97f9fae8b4400851cb | yes | 5 |
| | **Multipart Description/PDF files in .zip description** | | | | |
| | **Document Description** | | **Start** | **End** | |
| | Response After Final Action | | 1 | 1 | |
| | Claims | | 2 | 3 | |
| | Applicant Arguments/Remarks Made in an Amendment | | 4 | 5 | |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Transmittal Letter | Information_Disclosure_Statement.pdf | 26013<br>da539c1e7403834cd6bc1c5388302532363dbd38 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Information Disclosure Statement (IDS) Form (SB08) | Information_Disclosure_Statement_Fillable_PDF.pdf | 1035063<br>67259f63fd156054b5d1b5ec15590120561db86d | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems. | | | | | |
| 5 | Non Patent Literature | NPL_-_Extended_European_Search_Report_for_European_application_no_161523089_dated_July_1.pdf | 507281<br>9dc44c60c015f2a3998733ca051079a98d1535d7 | no | 7 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Fee Worksheet (SB06) | fee-info.pdf | 30011<br>0f05dc634e22162582301203d9302439df3cbffb | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | |
|---|---|
| **Total Files Size (in bytes):** | 2983974 |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 13/939,519 | 07/11/2013 | Leonard Luan C. Dang | C2081-701320 | 2110 |

94970 7590 10/14/2016

LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

| EXAMINER | |
|---|---|
| HIXSON, CHRISTOPHER | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1797 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 10/14/2016 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DOCKETING@LALaw.COM
pair_agios@firsttofile.com
CKent@LALaw.com

| Office Action Summary | Application No. 13/939,519 | Applicant(s) DANG ET AL. | |
|---|---|---|---|
| | Examiner Christopher A. Hixson | Art Unit 1797 | AIA (First Inventor to File) Status No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *9/15/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5)☒ Claim(s) *93-95 and 98-106* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *93-95 and 98-106* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

1. The present application is being examined under the pre-AIA first to invent provisions.

## DETAILED ACTION

2. The amendment dated 15 September 2016 is acknowledged. Claims 1-92, 96, and 97 are cancelled. Claims 100-106 are newly added. Therefore claims 93-95 and 98-106 are pending and considered on the merits below.

3. The rejection over written description is withdrawn. Other rejections over 35 USC 112 or 101 are maintained, as the amendment merely changes the precise grounds upon which the claims can be rejected. The rejection over prior art is withdrawn.

### *Priority*

4. Because no support for the correlation between mutants of IDH1 and IDH2 and 2HG neoactivity, required by all claims as filed, can be found in earlier priority documents, priority for claims including such a requirement are traced to US 61/173,518, filed 28 April 2009.

### *Claim Interpretation/Rejections - 35 USC § 112*

5. The examiner notes that the word "neoactivity" is defined by the applicant's specification. Provisional application 61/160,253 is incorporated by reference into the

present disclosure in [0001]. On p.3 of the '253 application, neoactivity is said to mean an activity which arises as a result of a mutation of an enzyme. In [0018] of the present specification, 2HG neoactivity is defined to "refer[] to the ability to convert alpha ketoglutarate to 2-hydroxyglutarate (sometimes referred to herein as 2HG)" because of the mutation of an enzyme.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. **Claims 93-95, 97-99 and 104-106** are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

With respect to the issue of enablement, attention is directed to the factors to be considered as laid out in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (see MPEP 2164).

***a. The breadth of the claims and the nature of the invention***

Regarding claim 93, one is to evaluate a subject for cancer (or cancer susceptibility) based on (at least) the result of an analysis the presence, distribution, or level of 2HG in a subject who does not have 2-HG aciduria.

In each of these claims, practically the only manipulative step required is a test for 2GH, the rest being mental or computational steps. As such, the claims are construed quite broadly.

***b. The state of the prior art***

The examiner notes that the prior art indicates that elevated 2HG can occur in conditions unrelated to that which the present invention concerns itself. For example, the Genetics Home Reference Website L2HGDH entry teaches that 2HG can become elevated in a different disorder unrelated to IDH (namely, an error in L-2-hydroxyglutarate dehydrogenase allows excess 2HG to accumulate). So the examiner concludes that elevated 2HG does not necessarily correlate with IDH 2HG neoactivity and especially not to cancer in general. Therefore, when the analyzing step includes simply determining the presence or level of 2HG, the examiner does not know how this can be distinguished between the correlation the applicant recites or some other known (or even unknown) correlation.

***c. The level of one of ordinary skill***

The skill is at the postgraduate level.

***d. The level of predictability in the art***

The examiner officially noted that molecular biology is a generally unpredictable field. Since this went unchallenged, it is not taken as admitted.

***e. The amount of direction provided by the inventor and the existence of working examples***

The examiner sees no guidance or working examples demonstrating enablement provided by the application on the issue he raises here.

***f. The quantity of experimentation needed***

Based on the analysis above, the examiner deems that an undue amount of experimentation would be required to practice the invention, as no guidance is provided to surmount the issue either in the art or by the applicant's disclosure.

## *Claim Rejections - 35 USC § 101*

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

**Claims 93-95 and 97-105** are rejected under 35 U.S.C. 101 because the claimed invention is directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more.

Claim(s) 93-105 is/are directed to a method which recites both an abstract idea and a natural law. Claim 93 is directed to the correlation of 2HG presence, distribution, or level in a particular type of subject and the "presence or susceptibility to cancer" in a

step in which the patient is said be “evaluated” (the correlation is a natural law, the implied diagnosis is an abstract idea).

The claim(s) does/do not include additional elements that are sufficient to amount to significantly more than the judicial exception.

Regarding claim 93, the analysis step is recited somewhat generically, and because it is a necessary step to gather information for the abstract idea and is otherwise necessary to make much use of the natural correlation, it cannot be said to add anything significantly more to the claim. Specifically, one is to measure the level "non-invasively by imaging or spectroscopic analysis." In a previous action, the examiner officially noted that MRI has been used to detect particular molecules in a subject (see the molecular MRI field), but this went unchallenged and so is taken as admitted. Additionally, the examiner cited to Sosnovik et al. (Curr Op Biotech 2007), pp.7-8, and this was further evidence that such is to be considered conventional by the examiner.

Even looking to the claim as a whole, the examiner sees nothing "significantly more" capable of conveying subject matter eligibility.

Dependent claims fail to add anything significantly more, and many simply raise new issues of subject matter eligibility.

Claims such as 94, 95, 100-103, and 105 simply appear to refine the natural law and/or the abstract idea claimed and therefore cannot be said to add something “significantly more."

Claims such as claims 98, 99 and 104 for example recite particulars of the analysis step, but do so in ways which remain entirely conventional. In a previous action, the examiner officially noted that MRI has been used to detect particular molecules in a subject (see the molecular MRI field), but this went unchallenged and so is taken as admitted. Additionally, the examiner cited to Sosnovik et al. (Curr Op Biotech 2007), pp.7-8, and this was further evidence that such is to be considered conventional by the examiner. That one must analyze “a tissue, product, or bodily fluid of the subject” scarcely limits the analysis step in any meaningful way. The examiner does not see that these limitations add something significantly more as is required when taken individually or when considering the claim as a whole.

### ***Response to Arguments***

9. Applicant's arguments filed 15 September 2016 have been fully considered but they are not persuasive.

The rejection over written description is withdrawn.

Regarding the rejection over enablement, the applicants argue that their amendment moots the rejection. The examiner disagrees, and points them to the detailed rejection above for his rationale. It is still not enabled to “evaluate the subject for cancer” because other causes exist which might provide the elevated levels of 2HG measured. To do such, it would appear, would require one to distinguish between these other causes and the recited cancer.

Regarding the rejection over 35 USC 101, the applicants assert that their claims “as a whole amounts to something significantly more than the judicial exception." In particular, they claim that their claim is limited to a "particular practical application." As evidence they indicate that the analysis step of claim 93 requires that one determine the level “non-invasively by imaging or spectroscopic analysis." As noted above, it was taken as admitted above that this is a conventional means of obtaining this information. The examiner also cited to additional evidence. Because the examiner previously had taken official notice, and this notice went unchallenged in the next reply, this was taken as admitted. It is insufficient now for the applicants to simply assert that the newly claimed feature “requires detection using an unconventional step" in the face of their previous admission and other facts provided by the applicant demonstrating the conventionality of the detection step.

The rejection over prior art is withdrawn.

***Conclusion***

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher A. Hixson whose telephone number is (571)270-5027. The examiner can normally be reached on M-F 9 am - 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lyle Alexander can be reached on (571)272-1254. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christopher A. Hixson/
Primary Examiner, Art Unit 1797

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | **Examiner** | **Art Unit** |
| | CHRISTOPHER A HIXSON | 1797 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/04/2015 | 06/02/2016 | 10/07/2016 | | | | | | |
| | 1 | - | - | - | | | | | | |
| | 2 | - | - | - | | | | | | |
| | 3 | - | - | - | | | | | | |
| | 4 | - | - | - | | | | | | |
| | 5 | - | - | - | | | | | | |
| | 6 | - | - | - | | | | | | |
| | 7 | - | - | - | | | | | | |
| | 8 | - | - | - | | | | | | |
| | 9 | - | - | - | | | | | | |
| | 10 | - | - | - | | | | | | |
| | 11 | - | - | - | | | | | | |
| | 12 | - | - | - | | | | | | |
| | 13 | - | - | - | | | | | | |
| | 14 | - | - | - | | | | | | |
| | 15 | - | - | - | | | | | | |
| | 16 | - | - | - | | | | | | |
| | 17 | - | - | - | | | | | | |
| | 18 | - | - | - | | | | | | |
| | 19 | - | - | - | | | | | | |
| | 20 | - | - | - | | | | | | |
| | 21 | - | - | - | | | | | | |
| | 22 | - | - | - | | | | | | |
| | 23 | - | - | - | | | | | | |
| | 24 | - | - | - | | | | | | |
| | 25 | - | - | - | | | | | | |
| | 26 | - | - | - | | | | | | |
| | 27 | - | - | - | | | | | | |
| | 28 | - | - | - | | | | | | |
| | 29 | - | - | - | | | | | | |
| | 30 | - | - | - | | | | | | |
| | 31 | - | - | - | | | | | | |
| | 32 | - | - | - | | | | | | |
| | 33 | - | - | - | | | | | | |
| | 34 | - | - | - | | | | | | |
| | 35 | - | - | - | | | | | | |
| | 36 | - | - | - | | | | | | |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | **Examiner** | **Art Unit** |
| | CHRISTOPHER A HIXSON | 1797 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/04/2015 | 06/02/2016 | 10/07/2016 | | | | | | |
| | 37 | - | - | - | | | | | | |
| | 38 | - | - | - | | | | | | |
| | 39 | - | - | - | | | | | | |
| | 40 | - | - | - | | | | | | |
| | 41 | ✓ | - | - | | | | | | |
| | 42 | ✓ | - | - | | | | | | |
| | 43 | ✓ | - | - | | | | | | |
| | 44 | ✓ | - | - | | | | | | |
| | 45 | ✓ | - | - | | | | | | |
| | 46 | ✓ | - | - | | | | | | |
| | 47 | ✓ | - | - | | | | | | |
| | 48 | ✓ | - | - | | | | | | |
| | 49 | ✓ | - | - | | | | | | |
| | 50 | ✓ | - | - | | | | | | |
| | 51 | ✓ | - | - | | | | | | |
| | 52 | ✓ | - | - | | | | | | |
| | 53 | ✓ | - | - | | | | | | |
| | 54 | ✓ | - | - | | | | | | |
| | 55 | ✓ | - | - | | | | | | |
| | 56 | ✓ | - | - | | | | | | |
| | 57 | N | - | - | | | | | | |
| | 58 | N | - | - | | | | | | |
| | 59 | N | - | - | | | | | | |
| | 60 | N | - | - | | | | | | |
| | 61 | N | - | - | | | | | | |
| | 62 | N | - | - | | | | | | |
| | 63 | ✓ | - | - | | | | | | |
| | 64 | ✓ | - | - | | | | | | |
| | 65 | ✓ | - | - | | | | | | |
| | 66 | N | - | - | | | | | | |
| | 67 | N | - | - | | | | | | |
| | 68 | N | - | - | | | | | | |
| | 69 | N | - | - | | | | | | |
| | 70 | N | - | - | | | | | | |
| | 71 | N | - | - | | | | | | |
| | 72 | N | - | - | | | | | | |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | **Examiner** | **Art Unit** |
| | CHRISTOPHER A HIXSON | 1797 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/04/2015 | 06/02/2016 | 10/07/2016 | | | | | | |
| | 73 | N | - | - | | | | | | |
| | 74 | N | - | - | | | | | | |
| | 75 | N | - | - | | | | | | |
| | 76 | N | - | - | | | | | | |
| | 77 | N | - | - | | | | | | |
| | 78 | N | - | - | | | | | | |
| | 79 | N | - | - | | | | | | |
| | 80 | ✓ | - | - | | | | | | |
| | 81 | ✓ | - | - | | | | | | |
| | 82 | ✓ | - | - | | | | | | |
| | 83 | ✓ | - | - | | | | | | |
| | 84 | ✓ | - | - | | | | | | |
| | 85 | ✓ | - | - | | | | | | |
| | 86 | ✓ | - | - | | | | | | |
| | 87 | ✓ | - | - | | | | | | |
| | 88 | ✓ | - | - | | | | | | |
| | 89 | ✓ | - | - | | | | | | |
| | 90 | ✓ | - | - | | | | | | |
| | 91 | ✓ | - | - | | | | | | |
| | 92 | ✓ | - | - | | | | | | |
| | 93 | ✓ | ✓ | ✓ | | | | | | |
| | 94 | ✓ | ✓ | ✓ | | | | | | |
| | 95 | ✓ | ✓ | ✓ | | | | | | |
| | 96 | ✓ | - | - | | | | | | |
| | 97 | ✓ | ✓ | - | | | | | | |
| | 98 | ✓ | ✓ | ✓ | | | | | | |
| | 99 | ✓ | ✓ | ✓ | | | | | | |
| | 100 | | ✓ | ✓ | | | | | | |
| | 101 | | ✓ | ✓ | | | | | | |
| | 102 | | ✓ | ✓ | | | | | | |
| | 103 | | ✓ | ✓ | | | | | | |
| | 104 | | ✓ | ✓ | | | | | | |
| | 105 | | ✓ | ✓ | | | | | | |
| | 106 | | ✓ | ✓ | | | | | | |

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | Examiner | Art Unit |
| | CHRISTOPHER A HIXSON | 1797 |

| CPC- SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| A61B5/055 | 26 may 2016 | cah |
| A61K31/41,426 | 26 may 2016 | cah |
| A61K45/06 | 26 may 2016 | cah |
| A61K2300/00 | 26 may 2016 | cah |
| C12N15/1137 | 26 may 2016 | cah |
| C12N2310/14 | 26 may 2016 | cah |
| C12Q1/32,6886 | 26 may 2016 | cah |
| C12Y101/01042 | 26 may 2016 | cah |
| G01N33/574 | 26 may 2016 | cah |
| G06F19/328 | 26 may 2016 | cah |

| CPC COMBINATION SETS - SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| US CLASSIFICATION SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

| SEARCH NOTES | | |
|---|---|---|
| Search Notes | Date | Examiner |
| searched in east as attached, inventor name search, google.com, scholar.google.com | 4 sept 2015 | cah |
| searched in east as attached, inventor name search, google.com, scholar.google.com | 26 may 2016 | cah |
| search in google as attached, inventor name search | 7 oct 2016 | cah |

| INTERFERENCE SEARCH |
|---|

| | |
|---|---|
| | |

| US Class/ CPC Symbol | US Subclass / CPC Group | Date | Examiner |
|---|---|---|---|
| | | | |

| | |
|---|---|
| | |

Google mri specific molecule

All Images News Videos Shopping More Search tools

About 674,000 results (0.82 seconds)

### Molecular magnetic resonance imaging
www.ncbi.nlm.nih.gov/.../PMC30976... National Center for Biotechnology Information
by A Hengerer - 2006 - Cited by 28 - Related articles
Apr 1, 2006 - Molecular MRI (mMRI) is a special implementation of Molecular Imaging for the ... Specific population of cells can be labeled with magnetic ...

### Molecular magnetic resonance imaging - Applied Radiology
appliedradiology.com/articles/molecular-magnetic-resonance-imaging
Jan 21, 2005 - Visualization of specific molecular events with magnetic resonance imaging (MRI) holds great promise for both clinical and basic science ...

### Molecular imaging - Wikipedia, the free encyclopedia
https://en.wikipedia.org/wiki/Molecular_imaging Wikipedia
Jump to **Magnetic resonance imaging (MRI)** - MRI has the advantages of having very high spatial resolution ... To achieve molecular imaging of disease biomarkers using ... In particular, the recent development of micron-sized ...

### MRI | Molecular Imaging
www.molecularimaging.com/.../magnetic-resonance-imaging MIR Preclininal Services
MRI is based on the phenomenon of nuclear magnetic resonance (NMR). Since the magnetic resonance properties of nuclei such as hydrogen nuclei (or ...

### Molecular magnetic resonance imaging in cancer | Journal of ...
https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-015-0659-x
by M Haris - 2015 - Related articles
Cancer Magnetic resonance Imaging Magnetic resonance spectroscopy ... Optical imaging has been used to image specific molecular features of cancer by ...

### Molecular Magnetic Resonance Imaging in Cardiovascular Medicine ...
circ.ahajournals.org/content/115/15/2076 Circulation
by DE Sosnovik - 2007 - Cited by 143 - Related articles
Apr 17, 2007 - Examples of 2 such recently used ligands include annexin for apoptosis imaging and a peptide specific for the vascular cell adhesion molecule ...

### [PDF] MRI Hyperpolarization and Molecular Imaging - Society of Nuclear ...
interactive.snm.org/.../MI_Gatew... Society of Nuclear Medicine and Molecular Imaging
Oct 6, 2013 - Hyperpolarized MRI and Other Molecular Imaging Modalities .... Studies using MBI and breast-specific γ-imaging have shown that these ...

### MRI, on a molecular scale | Harvard Gazette
news.harvard.edu/gazette/story/2014/.../mri-on-a-molecular-scale/ Harvard University
Apr 17, 2014 - Such efforts have long been hampered by the fact that they demand large quantities of a specific molecule, often in ordered and crystalized ...

### Molecular Imaging with MRI: Potential Application in Pancreatic Cancer
https://www.hindawi.com/journals/bmri/2015/624074/
by C Chen - 2015 - Related articles
Oct 4, 2015 - In recent years, the development of molecular imaging has made the specific targeting of PC in the early stage possible. Molecular imaging ...

### Molecular Magnetic Resonance Imaging of Tumors with a PTPμ ...
www.sciencedirect.com/science/article/pii/S1936523313800848 ScienceDirect
by SM Burden-Gulley - 2013 - Cited by 6 - Related articles
Molecular magnetic resonance imaging (MRI) of tumors improves the ... is a more specific MR molecular imaging probe than ProHance or a scrambled control.

## Searches related to mri specific molecule

**molecular imaging definition**

**molecular imaging chicago**

**pubmed**

**scholar**

Google magnetic resonance spectroscopy metabolomics in vivo

All News Images Videos Shopping More Search tools

Page 2 of about 218,000 results (0.42 seconds)

[PDF] A metabolomics perspective of human brain tumours
www.fast-mariecurie-rtn-project.eu/espacePrive/dvormondt/griffin07.pdf
by JL Griffin - 2007 - Cited by 95 - Related articles
This minireview focuses on metabolomics of human ... Keywords brain; metabolomics; NMR spectroscopy; .... Metabolomics in vivo using 1H MRS is limited by a.

nuclear magnetic resonance spectroscopy to define metabolomic ...
link.springer.com/article/10.1007/s13770-012-0016-6 Springer Science+Business Media
by SI Chun - 2012 - Cited by 3 - Related articles
The purpose of this study was to produce a metabolomic profile of a human ... CW Mun, JY Cho, WJ Shin, et al., Ex vivo proton MR spectroscopy (1H-MRS) for ...

Methodologies for Metabolomics: Experimental Strategies and Techniques
https://books.google.com/books?isbn=1139619055
Norbert W. Lutz, Jonathan V. Sweedler, Ron A. Wevers - 2013 - Medical
He, Q., et al., Single-scan in vivo lactate editing with complete lipid and water ... Leach, Phosphorus magnetic resonance spectroscopy on biopsy and in vivo, ...

[PDF] Evaluation of Cancer Metabolomics Using ex vivo High Resolution ...
www.mdpi.com/2218-1989/6/1/11/pdf MDPI
by TL Fuss - 2016 - Related articles
Mar 22, 2016 - Keywords: metabolomics; high-resolution magic angle spinning (HRMAS); ... Magnetic resonance spectroscopy (MRS), together with mass ...

In vivo mouse cardiac hyperpolarized magnetic resonance spectroscopy
https://jcmr-online.biomedcentral.com/articles/10.1186/1532-429X-15-19
by MS Dodd - 2013 - Cited by 20 - Related articles
Thus [1-$^{13}$C]pyruvate can be used to provide an in vivo cardiac metabolic ... metabolomic techniques, including $^{1}$H-nuclear magnetic resonance (NMR), gas ... $^{13}$C magnetic resonance spectroscopy (MRS) is particularly well suited to the ...

The Handbook of Metabonomics and Metabolomics
https://books.google.com/books?isbn=0080468004
John C. Lindon, Jeremy K. Nicholson, Elaine Holmes - 2011 - Science
Biochemical characterization of pediatric brain tumors by using in vivo and ex vivo magnetic resonance spectroscopy. J. Neurosurg. 2002;96:1023–1031. Natal ...

Frontiers | In vivo Magnetic Resonance Metabolic and ...
journal.frontiersin.org/article/10.3389/fonc.2016.00164
by R Canese - 2016 - Cited by 1
Jun 28, 2016 - Magnetic resonance spectroscopy (MRS) is a non-invasive imaging method that ... Typical in vivo $^{1}$H MRS spectra acquired at 4.7 T from vital areas (as detected ..... Magnetic resonance spectroscopy detectable metabolomic ...

In vivo and ex vivo magnetic resonance spectroscopy of the ... - PubPDF
www.pubpdf.com/.../In-vivo-and-ex-vivo-magnetic-resonance-spectroscopy-of-the-i...
May 21, 2015 - Evaluation of Cancer Metabolomics Using ex vivo High Resolution Magic Angle Spinning (HRMAS) Magnetic Resonance Spectroscopy (MRS).

Live-cell high resolution magic angle spinning magnetic resonance ...
https://www.spandidos-publications.com/br/1/5/707
by V Righi - 2013 - Cited by 5 - Related articles
Jul 22, 2013 - ... high resolution magic angle spinning magnetic resonance spectroscopy for in vivo analysis of Pseudomonas aeruginosa metabolomics.

Proteomic and Metabolomic Approaches to Biomarker Discovery
https://books.google.com/books?isbn=0123947952
Haleem J Issaq, Timothy D. Veenstra - 2013 - Science
Determining the in vivo regulation of cardiac pyruvate dehydrogenase based on label flux ... Magnetic resonance imaging with hyperpolarized 1,4-13C2 fumarate allows detection ... Molecular imaging of cancer: MR spectroscopy and beyond

Searches related to magnetic resonance spectroscopy metabolomics in

vivo

magnetic resonance spectroscopy **for temporal meningioma benign**

magnetic resonance spectroscopy **brain**

**nuclear** magnetic resonance spectroscopy

magnetic resonance **imaging** spectroscopy

magnetic resonance spectroscopy **for temporal meningioma benign cpt code**

magnetic resonance spectroscopy **identifies neural progenitor cells** in **the live human brain**

magnetic resonance spectroscopy **ppt**

magnetic resonance spectroscopy **definition**

Previous 1 2 3 4 5 6 7 8 9 10 Next

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: September 15, 2016
Electronic Signature for Asimina T. Georges Evangelinos: /Asimina T. Georges Evangelinos/

Docket No.: C2081-701320
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Leonard Luan C Dang et al.

Application No.: 13/939,519 | Confirmation No.: 2110

Filed: July 11, 2013 | Art Unit: 1797

For: METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | Examiner: C. Hixson

**AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111**

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

**INTRODUCTORY COMMENTS**

In response to the Office Action dated June 16, 2016, please amend the above-identified U.S. patent application as follows:

**Amendments to the Claims** begin on page 2 of this paper.

**Remarks/Arguments** begin on page 4 of this paper.

An Information Disclosure Statement is being filed with this paper.

## AMENDMENTS TO THE CLAIMS

*Please replace all previously filed claims for the application with the following listing of claims:*

Listing of the Claims:

1-92. (Canceled)

93. (Currently Amended) A method of evaluating a subject for the presence or susceptibility to a cancer comprising analyzing the subject or a sample from the subject for the presence, distribution, or level of 2HG non-invasively by imaging or spectroscopic analysis, wherein the subject does not have or is not diagnosed as having 2-hydroxyglutaric aciduria, and wherein the cancer is characterized by a mutant IDH enzyme having a neoactivity, thereby evaluating the subject for such cancer.

94. (Previously Presented) The method of claim 93, wherein the cancer is selected from the group consisting of an astrocytic tumor, an oligodendroglial tumor, an oligoastrocytic tumor, an anaplastic astrocytoma, fibrosarcoma, paraganglioma, prostate cancer, acute lymphoblastic leukemia, and acute myelogenous leukemia.

95. (Previously Presented) The method of claim 93, wherein the cancer is a glioblastoma.

96. - 97 (Cancelled)

98. (Currently Amended) The method of claim [[97]]93, wherein the imaging or spectroscopic analysis comprises magnetic resonance imaging or magnetic resonance spectroscopy.

99. (Previously Presented) The method of claim 93, wherein the presence, distribution or level of 2HG is determined by evaluating a tissue, product or bodily fluid of the subject.

100. (Previously Presented) The method of claim 93, wherein the cancer is characterized by a somatic allele, which encodes a mutant IDH enzyme having a neoactivity.

101. (Previously Presented) The method of claim 100, wherein the mutant IDH enzyme is IDH1.

102. (Previously Presented) The method of claim 101, wherein the mutant IDH1 enzyme is selected from the group consisting of R132H, R132C, R132S, R132G, R132L, and R132V.

103. (Previously Presented) The method of claim 100, wherein the mutant IDH enzyme is IDH2.

102. (Previously Presented) The method of claim 100, wherein the mutation is an IDH2 mutation.

103. (Previously Presented) The method of claim 102, wherein the IDH2 mutation is selected from the group consisting of R172K, R172M, R172S, R172G, and R172W.

104. (Previously Presented) The method of claim 93, wherein detecting the presence of 2HG in a subject by magnetic resonance spectroscopy indicates the presence of a cancer in the subject.

105. (Previously Presented) The method of claim 104, wherein the cancer is a glioma.

106. (Previously Presented) The method of claim 104, wherein the presence or level of 2HG by magnetic resonance spectroscopy is indicated by a signal at about 2.5ppm.

## REMARKS

Claims Status

Claims 93-95 and 97-106 are pending in the application. Claim 97 is cancelled. Claim 93 is amended and recites a method of evaluating a subject for the presence or susceptibility to a cancer comprising analyzing the subject or a sample from the subject for the presence, distribution, or level of 2HG non-invasively by imaging or spectroscopic analysis, wherein the subject does not have or is not diagnosed as having 2-hydroxyglutaric aciduria, and wherein the cancer is characterized by a mutant IDH enzyme having a neoactivity, thereby evaluating the subject for such cancer. Support for the amendment to claim 93 can be found, *e.g.*, at least in cancelled claim 97 and at page 7 of the application as filed. Upon entry of the amendment, claims 93-95 and 98-106 will be pending. No new matter has been added by this amendment.

Rejections under 35 U.S.C. § 112, first paragraph

I. Claim 93-95, 97-99 and 104-106 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The Office contends that while the specification discloses particular cancers having elevated levels of 2HG, the specification does not disclose diagnosing all cancers having elevated 2HG levels. Solely to expedite prosecution of this application, Applicants have amended claim 93 to recite that the cancer is characterized by a mutant IDH enzyme having a neoactivity. As such, the claims do not recite diagnosing all cancers having elevated 2HG levels. Accordingly, claim 93 and its dependent claims 94-95, 97-99 and 104-106 are supported by the specification, and Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

II. Claims 93-95, 97-99 and 104-106 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. In particular, the Office contends that the claims are broad and that elevated 2HG does not necessarily correlate with IDH 2HG neoactivity and cancer in general. Solely to expedite prosecution of this application, Applicants have amended claim 93 to recite that the cancer is characterized by a mutant IDH enzyme having a neoactivity. Applicants submit that the claims are enabled for at least the reason that the specification provides data for evaluating 2HG

levels in cell lines expressing a mutant IDH enzyme having 2HG neoactivity. See, *e.g.*, the examples on pages 99-120 of the application as filed. Accordingly, the rejection of claim 93 and dependent claims 94-95, 97-99 and 104-106 under 35 U.S.C. § 112, first paragraph should be withdrawn.

Rejection under 35 U.S.C. § 101

Claims 93-95 and 97-105 are rejected under 35 U.S.C. § 101 as allegedly being directed to subject matter that is not patent eligible. The Office contends that the claims recite an abstract idea, *i.e.*, a judicial exception, without significantly more, and therefore the claims are not patent eligible. Applicants submit that the claims recite something significantly more than an abstract idea, and are thus directed toward patent eligible subject matter. Applicants respectfully traverse the rejection for the following reasons.

Claim 93 recites a method of evaluating a subject for the presence or susceptibility to a cancer comprising analyzing the subject or a sample from the subject for the presence, distribution, or level of 2HG non-invasively by imaging or spectroscopic analysis, wherein the subject does not have or is not diagnosed as having 2-hydroxyglutaric aciduria, and wherein the cancer is characterized by a mutant IDH enzyme having a neoactivity, thereby evaluating the subject for such cancer. Applicants submit that amended claim 1 is patent eligible for at least the reason that the claim as a whole amounts to significantly more than the judicial exception.

According to the May 5, 2016 and July 30, 2015 updates to the *2014 Interim Guidance on Patent Subject Matter Eligibility* (hereafter "Guidance") a claim is patent eligible if the claim "**as a whole amounts to significantly more than the judicial exception when the additional elements are considered both individually and in combination**." Further, the Office states that "when an additional element is considered individually by the examiner, the additional element may be enough to qualify as 'significantly more' if it meaningfully limits the judicial exception." The Office illustrates how claims should be analyzed under the Guidance by providing specific examples. In Example 29, the Office provides a hypothetical example illustrating the application of the significantly more analysis to diagnostic and treatment claims using the hypothetical disease, "Julitis." The Office provides hypothetical claims 3 and 4, which recite a method of diagnosing

Julitis, which are indicated as patent eligible. In particular, the Office provides that hypothetical claim 3 is patent eligible because the claim further requires detecting using an unconventional step that is more than a mere instruction to "apply" the correlation and critical thinking step, *i.e.*, the use of a porcine anti-JUL-1 antibody. Similarly, the Office indicates that hypothetical claim 4 is eligible because it further requires detecting using the unconventional step of using antibody mAb-D33 to detect the presence of JUL-1 in a plasma sample.

Applicants submit that similar to hypothetical claims 3 and 4, amended claim 1 is patent eligible because the claim **as a whole amounts to significantly more than the judicial exception**. The additional element of determining 2HG levels non-invasively by imaging or spectroscopic analysis, requires detection using an unconventional step. This additional element when considered in the claim as a whole amounts to significantly more than the judicial exception. As such, amended claim 93 and dependent claims 94-95 and 97-105 are patent eligible and the rejection under 35 U.S.C. §101 should be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 93-95, 99, and 105 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Struys *et al.* (Clinical Chemistry 2004) ("Struys") as evidenced by Aghili *et al.* J. Neurooncology 91, 233-6 (2009) ("Aghili"). Applicants have amended claim 93 to recite that the cancer to be treated is characterized by a mutant IDH enzyme having a neoactivity. Further, claim 93 is amended to recite that 2HG levels are determined non-invasively by imaging or spectroscopic analysis, which is recited in claim 97 (now cancelled), which is not rejected. Struys as evidenced by Aghili does not disclose a method of evaluating a subject for the presence or susceptibility to a cancer comprising analyzing the subject or a sample from the subject for the presence, distribution, or level of 2HG non-invasively by imaging or spectroscopic analysis, wherein the subject does not have or is not diagnosed as having 2-hydroxyglutaric aciduria, and wherein the cancer is characterized by a mutant IDH enzyme having a neoactivity. As such, Struys as evidenced by Aghili does not anticipate claim 93 and dependent claims 94-95, 99 and 105. Accordingly, the rejection under 35 U.S.C. § 102(b) should be withdrawn.

## CONCLUSION

In view of the foregoing amendments and remarks, reconsideration is respectfully requested. This application should now be in condition for allowance; a notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee that is not covered by an accompanying payment, please charge any deficiency to Deposit Account No. 50/2762; Our Ref. C2081-701320.

Dated: September 15, 2016

Respectfully submitted,

By: /Asimina T. Georges Evangelinos/
Asimina T. Georges Evangelinos
Registration No.: 66,888
LANDO & ANASTASI LLP
Riverfront Office Park
One Main Street
Suite 1100
Cambridge, Massachusetts 02142
(617) 395-7000
Attorney/Agent for Applicant

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: September 15, 2016
Electronic Signature for Asimina T. Georges Evangelinos: /Asimina T. Georges Evangelinos/

Docket No.: C2081-701320
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Lenny Dang et al.

Application No.: 13/939,519 | Confirmation No.: 2110

Filed: July 11, 2013 | Art Unit: 1797

For: METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | Examiner: C. Hixson

**INFORMATION DISCLOSURE STATEMENT (IDS)**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed more than three months after the filing date of this application, OR more than three months after the date of entry of the national stage in the international application, AND after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R.§ 1.113, a Notice of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith are copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Please charge our Deposit Account No. 50/2762 in the amount of $180.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 50/2762, under Order No. C2081-701320.

Dated: September 15, 2016

Respectfully submitted,

By: /Asimina T. Georges Evangelinos/
Asimina T. Georges Evangelinos
Registration No.: 66,888
Catherine M. McCarty
Registration No.: 54,301
LANDO & ANASTASI, LLP
Riverfront Office Park
One Main Street, Suite 1100
Cambridge, Massachusetts 02142
(617) 395-7000
Attorneys for Applicant

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE



# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Lenny Dang |
| Art Unit | 1797 |
| Examiner Name | C. Hixson |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 5021421 | | 1991-06-04 | Hino et al. | |
| | 2 | 5807876 | | 1998-09-15 | Armistead et al. | |
| | 3 | 5965569 | | 1999-10-12 | Camps Garcia et al. | |
| | 4 | 6262113 | | 2001-07-17 | Widdowson et al. | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 20020188027 | A1 | 2002-12-12 | Robinson et al. | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Lenny Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 101296909 | CN | A | 2008-10-29 | Serono Lab | | ☒ |
| | 2 | 0022958 | EP | A1 | 1981-01-28 | Bayer Ag | | ☐ |
| | 3 | 1996030343 | WO | A1 | 1996-10-03 | Merck & Co., Inc | | ☐ |
| | 4 | 1997044322 | WO | A1 | 1997-11-27 | Chiroscience Ltd | | ☐ |
| | 5 | 2001019788 | WO | A2 | 2001-03-22 | Cor Therapeutics, Inc | | ☐ |
| | 6 | 2001019798 | WO | A2 | 2001-03-22 | Cor Therapeutics Inc | | ☐ |
| | 7 | 2001064642 | WO | A2 | 2001-09-07 | Cor Therapeutics, Inc | | ☐ |
| | 8 | 2001064643 | WO | A2 | 2001-09-07 | Cor Therapeutics, Inc | | ☐ |
| | 9 | 2002100822 | WO | A1 | 2002-12-19 | Biovitrum Ab | | ☐ |
| | 10 | 2004089470 | WO | A2 | 2004-10-21 | Novo Nordisk As | | ☐ |
| | 11 | 2005120474 | WO | A2 | 2005-12-22 | Leuven K U Res & Dev | | ☐ |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Lenny Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 12 | 2006034341 | WO | A2 | 2006-03-30 | Xenon Pharmaceuticals Inc | | ☐ |
| | 13 | 2007003934 | WO | A2 | 2007-01-11 | Sterix Ltd | | ☐ |
| | 14 | 2008052190 | WO | A2 | 2008-05-02 | Flynn, Gary et al. | | ☐ |
| | 15 | 2008073670 | WO | A2 | 2008-06-19 | Millennium Pharmaceuticals, Inc | | ☐ |
| | 16 | 2009126863 | WO | A2 | 2009-10-15 | Genentech, Inc | | ☐ |
| | 17 | 2010/129596 | WO | A1 | 2010-11-11 | Agios Pharmaceuticals, Inc | | ☐ |
| | 18 | 2010130638 | WO | A1 | 2010-11-18 | Evotec Ag | | ☐ |
| | 19 | 2011032169 | WO | A2 | 2011-03-17 | Phusis Therapeutics Inc | | ☐ |
| | 20 | 2011047432 | WO | A1 | 2011-04-28 | Fibrotech Therapeutics Pty Ltd | | ☐ |
| | 21 | 2012/092442 | WO | A1 | 2012-07-05 | Agios Pharmaceuticals, Inc | | ☐ |
| | 22 | 2012151452 | WO | A1 | 2012-11-08 | Agios Pharmaceuticals, Inc | | ☐ |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Lenny Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 23 | 97/28128 | WO | A1 | 1997-08-07 | Zeneca Ltd | | ☐ |
| | 24 | 9932463 | WO | A1 | 1999-07-01 | Bayer Ag | | ☐ |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T5 |
|---|---|---|---|
| | 1 | International Preliminary Report for related application No. PCT/US2011/067752 dated April 11, 2013 | |
| | 2 | International Search Report dated March 5, 2012 for related international application no. PCT/US2011/067752. | |
| | 3 | REGISTRY (STN) [online], 2006.08.23 [Retrieved on 2016.01.29] CAS Registration No. 903862-76-0 | |
| | 4 | REGISTRY (STN) [online], 2006.08.23 [Retrieved on 2016.01.29] CAS Registration No. 903869-26-1 | |
| | 5 | REGISTRY (STN) [online], 2007.04.13 [Retrieved on 2016.01.29] CAS Registration No. 929819-92-1 | |
| | 6 | REGISTRY (STN) [online], 2007.04.13 [Retrieved on 2016.01.29] CAS Registration No. 929971-43-7 | |
| | 7 | REGISTRY (STN) [online], 2009.04.19 [Retrieved on 2016.01.29] CAS Registration No. 1136498-70-8 | |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Lenny Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 8 | REGISTRY (STN) [online], 2009.08.27 [Retrieved on 2016.01.29] CAS Registration No. 1176756-98-1 | |
| | 9 | STN Tokyo, Registry Number 1001833-18-6, Entered STN on February 6, 2008, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [(4-methyl-l-piperazinyl)carbonyl]phenyl]–" | |
| | 10 | STN Tokyo, Registry Number 1030142-35-8, Entered STN on June 24, 2008, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-[(5-methyl-3-isoxazolyl)methyl]-l-piperazinyl]carbonyl]phenyl]-" | |
| | 11 | STN Tokyo, Registry Number 1031531-78-8, Entered STN on June 29, 2008 Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, N-4[4-[(4-acetyl-1-piperazinyl)carbonyl]phenyl]-2,3-dihydro-" | |
| | 12 | STN Tokyo, Registry Number 1057928-35-4, Entered STN on October 7, 2008, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(2-pyridinyl)-l-piperazinyl]carbonyl]phenyl]-" | |
| | 13 | STN Tokyo, Registry Number 1240875-006, entered STN on September 14, 2010, Chemical Abstracts Index Name '1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4-[[4-(2-thiazolyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 14 | STN Tokyo, Registry Number 748791-86-8, Entered STN on September 21, 2004, Chemical Abstracts Index Name '1,4-Benzodioxin-6-sulfonamide, N-[4- [[4-(2-furanylcarbonyl)-1-piperazinyl]carbonyl]phenyl]-2,3-dihydro-" | |
| | 15 | STN Tokyo, Registry Number 878469-24-0, Entered STN on March 29, 2006, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4-[[4-(2-pyrimidinyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 16 | STN Tokyo, Registry Number 878474-39-6, Entered STN on March 29, 2006, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4[(4-phenyl-1-piperazinyl)carbonyl]phenyl]-" | |
| | 17 | STN Tokyo, Registry Number 878590-33-1, Entered STN on March 30, 2006, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4-{{4-(tetrahydro-2-furanyl)methyl]-1-piperazinyl]carbonyl]phenyl]-" | |
| | 18 | STN Tokyo, Registry Number 878943-66-9 Entered STN on April 2, 2006, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 3,4-dihydro-N-[[4-(2-pyrimidinyl)-1-piperazinyl)carbonyl]phenyl]-" | |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Lenny Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 19 | STN Tokyo, Registry Number 878956-06-0, Entered STN on April 2, 2006, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, N-[4- [[4-(cyclopropylcarbonyl)-1-piperazinyl]carbonyl]phenyl]-2,3-dihydro-" | |
| | 20 | STN Tokyo, Registry Number 9200679-46-5, Entered STN on February 13, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(4-pyridinyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 21 | STN Tokyo, Registry Number 920822-52-2, Entered STN on February 14, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, N-[4- [[4-(4-fluoropheyl)-1-piperazinyl]carbonyl]phenyl] - 2,3dihydro-" | |
| | 22 | STN Tokyo, Registry Number 920824-56-2, Entered STN on February 14, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(3-thienylmethyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 23 | STN Tokyo, Registry Number 920847-34-3, Entered STN on February 14, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(2-methylphenyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 24 | STN Tokyo, Registry Number 920875-39-4, Entered STN on February 14, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(2-hydroxyphenyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 25 | STN Tokyo, Registry Number 920902-88-1, Entered STN on February 14, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(2-thienylmethyl)-l-piperazinyl]carbonyl]phenyl]-" | |
| | 26 | STN Tokyo, Registry Number 920921-09-1 Entered STN on February 14, 2007, Chemical Abstracts Index Name "2H-1, 5-Benzodioxepin-7-sulfonamide, 3,4-dihydro-N-[4-[[4-(2pyridinyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 27 | STN Tokyo, Registry Number 920924-42-1, Entered STN on February 14, 2007, Chemical Abstracts Index Name "1,4-Benzodioxin-6-sulfonamide, 2,3-dihydro-N-[4- [[4-(2-pyridinylmethyl)-1-piperazinyl]carbonyl]phenyl]-" | |
| | 28 | STN Tokyo, Registry Number 941220-77-5, Entered STN on July 4, 2007, Chemical Abstracts Index Name "2H-1, 5-Benzodioxepin-7-sulfonamide, 3,4-dihydro-N-[4-[(4-methyl-l-piperazinyl)carbonyl]phenyl]-" | |
| | 29 | Lutker et al, "Crystal Polymorphism in a Carbamazepine Derivative: Oxcarbazepine". NIH Public Access. J Pharm Sci. 2010 February ; 99(2): 794-803. doi: 10.1002/jps.21873 | |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Lenny Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | |
|---|---|---|
| | 30 | Rao et al., "Polymorphism in Drugs and its Significance in Therapeutics". Journal of Scientific & Industrial Research Vol. 46 October 1987 pp 450-455. |
| | 31 | Docoslis et al., "Characterization of the Distribution, Polymorphism, and Stability of Nimodipine in Its Solid Dispersions in Polyethylene Glycol by Micro-Raman Spectroscopy and Powder X-Ray Diffraction". The AAPS Journal 2007; 9 (3) Article 43, E361-E370. |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Lenny Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| Signature | /Asimina T. Georges Evangelinos/ | Date (YYYY-MM-DD) | 2016-09-15 |
|---|---|---|---|
| Name/Print | Asimina T. Georges Evangelinos | Registration Number | 66,888 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>C2081-7035WO | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/US2011/067752 | International filing date *(day/month/year)*<br>29.12.2011 | Priority date *(day/month/year)*<br>29.12.2010 |
| International Patent Classification (IPC) or national classification and IPC<br>INV. A61K31/496 | | |
| Applicant<br>Agios Pharmaceuticals, Inc. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 8 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions).
      ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2).
      ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)).
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3*bis* of Annex C of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 26.10.2012 | 11.04.2013 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Terenzi, Carla<br>Telephone No. +49 89 2399-7707 |

Form PCT/IPEA/409 (Cover Sheet) (July 2011)

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

International application No.
PCT/US2011/067752

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-156 as originally filed

   **Claims, Numbers**

   1-17 filed with telefax on 26-10-2012

   ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:

5. ☐ This report has been established:
   - ☐ taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
   - ☐ without taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

6. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-17 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 13 |
| | No: | Claims | 1-12, 14-17 |
| Industrial applicability (IA) | Yes: | Claims | 1-17 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

## Re Item I

### Basis of the report

### 1. Amendments

The amendment filed with the letter dated 26.10.2012 does not introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. Basis for claim 1 can be found on page 12, line 16 of the specification as originally filed.

## Re Item V

### Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Claims 15 and 16 relate to a subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT. Their patentability is *inter alia* dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT.The EPO, for example, does not recognise as patentable claims to the use of a compound in a medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

### 2. Novelty

None of the documents of the prior art explicitly discloses compounds falling within general formula (I). Therefore, the subject-matter of claims 1-17 is new in the sense of Article 33(2) PCT.

### 3. Inventive step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-12 and 14-17 does not involve an inventive step in the sense of Article 33(3) PCT.

Document D2 is regarded as being the prior art closest to the subject-matter of the present application, and discloses benzene sulfonamide derivatives and their use in the treatment of cancer.

The main difference between the compounds of present formula (I) and example 130 of D2 resides in the presence of a carbonyl group instead of a methylene group between the piperazine and the benzenesulfonamide moieties. Example 146 of D2 differs form the compound of formula (I) in that the phenyl ring is meta and not para substituted. Moreover, both the compound recited in Example 130 and the compound recited in example 146 contain a sulfonamide moiety that is reversed when compared to formula (I) (i.e., the sulfonamide nitrogen in formula (I) is connected to the central phenyl ring).

The objective technical problem to be solved may therefore be regarded as the provision of alternative compounds for use in the treatment of cancer.

In view of the structural differences mentioned above, the current application is not considered to represent an obvious equivalent, analogue or modification of the compounds known from D2.

However, an inventive step can presently not be acknowledged for the subject-matter of claims 1-12 and 14-17 for the following reasons:

The present application fails to prove that all the claimed compounds solve the problem posed. As a matter of fact, Table 4 shows that compounds 117 and 451 do not possess the ability to activate PKM2; moreover, no data are available for compounds 224 and 225.

Therefore, since in order to fulfil the requirements of Article 33(3) PCT, it is foreseen that the claimed invention is based on a technical effect achieved over the whole scope of the claims, no inventive step can be acknowledged for the subject matter of the present application.

Claim 13 appears to be novel and inventive over the available prior art documents.

## Re Item VIII

### Certain observations on the international application

1. Claim 12 is directed to the compounds of Tables 2 and 3. However, no compound is listed in said Tables.

2. Claim 15 defines the therapeutic application of the compounds of formula (I) only in functional terms *"method of activating PKM2"*, which do not allow any practical application in the form of a defined, real treatment of a pathological condition. The subject-matter of said claim is therefore unclear, contrary to the requirements of Article 6 PCT.

Docket No.: C2081-7035WO

**IN THE EUROPEAN PATENT AND TRADEMARK OFFICE**
**AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY**
**(IPEA/EP)**

| | | |
|---|---|---|
| International Application No. | : | PCT/US2011/067752 |
| International Filing Date | : | 29 December 2011 (29.12.2011) |
| Earliest Priority Date | : | 29 December 2010 (29.12.2010) |
| Applicant | : | Agios Pharmaceuticals, Inc. |
| Title | : | THERAPEUTIC COMPOUNDS AND COMPOSITIONS |

**AMENDMENT UNDER PCT RULE 34**
**RESPONSE TO WRITTEN OPINION OF ISA**

European Patent Office
P.B. 5818 Patentlaan 2
NL 2280 HV Rijswijk

Authorized Officer: Carla Terenzi

Dear Sirs:

In response to the Written Opinion mailed on 5 March 2012, Applicant amends the application as shown in the attached substitute claims. Claims 1-17 are substituted for original claims 1-17. Accordingly, substitute claims 1-17 are pending for examination.

The differences between the substitute claims and the claims as originally filed are as follows:

Claim 1 is amended to define Q as $NR^b$ and $Q^1$ as a bond. The basis for this amendment can be found on p. 12, line 16 of the specification as originally filed.

Claim 9 is amended to remove recitation of "and $Q^1$ is a bond".

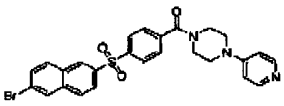
## REMARKS

### I. Status of the Claims

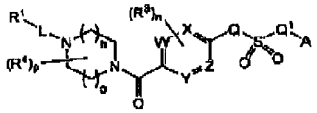
The Written Opinion has been established with respect to claims 1-17. Claims 2-6, 8, 9, 12, 13 and 15-17 were found to possess novelty in accordance with PCT Article 33(2). Claims 1, 7, 10, 11 and 14 were found to lack novelty in accordance with PCT Article 33(2). Claims 1-17 were found to lack inventive step under PCT Article 33(3). Claims 1-12 were found to possess industrial applicability in accordance with PCT Article 33(4).

### II. Claims 1-17 Possess Novelty

Original claims 1, 7, 10, 11 and 14 were found to lack novelty in view of D1 (U.S. Publication No. 2003/0207882). D1 discloses the following compound cited in the written opinion:



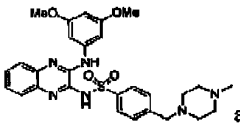
; along with other sulphonyl compounds. In contrast, Independent claim 1, as amended, recites a compound of formula (I):

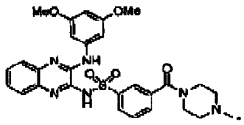


(I) wherein Q is $NR^b$ and $Q^1$ is a bond. In view of this, none of the compounds in D1 fall within the scope of amended claim 1 (or its dependent claims). Accordingly, Applicant respectfully requests reconsideration and withdrawal of the novelty objection.

### III. Claims 1-17 Possess Inventive Step

Original claims 1-17 were found to lack inventive step in view of D2 (WO 2007/023186), specifically, in view of Examples 130 and 146 of D2. Example 130 discloses a compound of the following formula:


and example 146 discloses the following compound:


. The written opinion acknowledges that these compounds do not fall within the scope of formula (I) as Example 130 does not contain a central carbonyl linker while Example 146 contains a meta substitution pattern on its central phenyl ring in contrast to the para substitution pattern recited for formula (I) compounds. In view of the amendments to claim 1, the compounds recited in Examples 130 and 146 also contain a sulfonamide moiety that is reversed when compared to formula (I) (i.e., the sulfonamide nitrogen in formula (I) is connected to the central phenyl ring). In fact, none of the compounds disclosed in D2 contain this "reversed" sulphonamide substitution pattern. Accordingly, the skilled artisan would have no motivation to modify D2 in order to arrive at the compounds recited in amended claim 1. In light of this, Applicant respectfully requests reconsideration and withdrawal of the inventive step objection of claims 1-17.

## IV. Conclusion

In light of the amendments and accompanying remarks submitted herein, Applicant submits that claims 1-17 are novel and inventive.

Dated: 29 October 2012

Respectfully submitted,

By

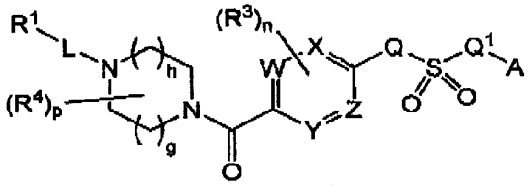
Peter Korakas
LANDO & ANASTASI LLP
Riverfront Office Park
One Main Street
Suite 1100
Cambridge, Massachusetts 02142
(617) 395-7000
Attorney for Applicant

**Application No.: PCT/US2011/067752** **Docket No.: C2081-7035WO**

**Substitute Claims (Clean Copy)**

**What is claimed is:**

1. A compound of formula (I):



(I), or a pharmaceutically acceptable salt thereof wherein:

W, X, Y and Z are each independently selected from CH or N;

Q is $NR^b$;

$Q^1$ is a bond;

A is optionally substituted bicyclic aryl or optionally substituted bicyclic heteroaryl;

L is a bond, -C(O)-, $-(CR^cR^c)_m$-, -OC(O)-, $-(CR^cR^c)_m$-OC(O)-, $-(CR^cR^c)_m$-C(O)-, $-NR^bC(S)$-, or $-NR^bC(O)$- (wherein the point of the attachment to $R^1$ is on the left-hand side);

$R^1$ is selected from alkyl, carbocycle, aryl, heteroaryl, and heterocyclyl; each of which is substituted with 0-5 occurrences of $R^d$;

each $R^3$ is independently selected from halo, haloalkyl, alkyl, hydroxyl and $-OR^a$, or two adjacent $R^3$ taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;

each $R^4$ is independently selected from halo, haloalkyl, alkyl, hydroxyl, =O, $-OR^a$ and phenyl, or two $R^4$ taken together with the carbon atoms to which they are attached form a bridged, fused or spyro-fused carbocycle, an aryl or a heteroaryl;

each $R^a$ is independently selected from alkyl, acyl, hydroxyalkyl and haloalkyl;

each $R^b$ is independently selected from hydrogen and alkyl;

each $R^c$ is independently selected from hydrogen, halo, alkyl, alkoxy and halo alkoxy or two $R^c$ taken together with the carbon atoms to which they are attached form an optionally substituted cycloalkyl;

each $R^d$ is independently selected from halo, haloalkyl, haloalkoxy, alkyl, alkynyl, nitro, cyano, hydroxyl, $-C(O)R^a$, $-OC(O)R^a$, $-C(O)OR^a$, $-SR^a$, $-NR^aR^b$ and $-OR^a$, or two $R^d$ taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;

n is 0, 1, or 2;

m is 1, 2 or 3;

h is 0, 1, 2;

g is 0, 1 or 2;

the sum of g + h is equal to or greater than 2; and

p is 0, 1 or 2; and provided that the compound of formula (I) is not

N-[3-[(3,5-dimethoxyphenyl)amino]-2-quinoxalinyl]-4-[(4-methyl-1-piperazinyl)carbonyl]- benzenesulfonamide;

N-[4-[[4-(2-furanylmethyl)-1-piperazinyl]carbonyl]phenyl]-2,3-dihydro-2-oxo-1H-benzimidazole-5-sulfonamide;

2,3-dihydro-2-oxo-N-[4-[[4-(2,2,2-trifluoroethyl)-1-piperazinyl]carbonyl]phenyl]-1H-benzimidazole-5-sulfonamide;

2,3-dihydro-N-[4-[[4-(4-nitrophenyl)-1-piperazinyl]carbonyl]phenyl]-2-oxo-1H-benzimidazole-5-sulfonamide;

N-[4-[[4-(2-ethoxyphenyl)-1-piperazinyl]carbonyl]phenyl]-2,3-dihydro-2-oxo-1H-benzimidazole-5-sulfonamide;

2,3-dihydro-2-oxo-N-[4-[[4-(3-thienylmethyl)-1-piperazinyl]carbonyl]phenyl]-1H-benzimidazole-5-sulfonamide;

N-[4-[[4-(2,3-dimethylphenyl)-1-piperazinyl]carbonyl]phenyl]-2,3-dihydro-2-oxo-1H-benzimidazole-5-sulfonamide;

2,3-dihydro-N-[4-[[4-(2-hydroxyphenyl)-1-piperazinyl]carbonyl]phenyl]-2-oxo-1H-benzimidazole-5-sulfonamide;

4-[4-[[(2,3-dihydro-2-oxo-1H-benzimidazol-5-yl)sulfonyl]amino]benzoyl]-1-piperazinecarboxylic acid ethyl ester;

**Application No.: PCT/US2011/067752** **Docket No.: C2081-7035WO**

N-[4-[(4-acetyl-1-piperazinyl)carbonyl]phenyl]-2,3-dihydro-2-oxo-1H-benzimidazole-5-sulfonamide;

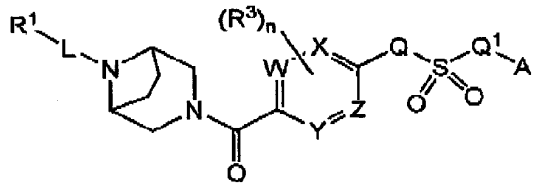
N-[4-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]phenyl]-2,3-dihydro-2-oxo-1H-benzimidazole-5-sulfonamide;

2,3-dihydro-2-oxo-N-[4-[(4-phenyl-1-piperazinyl)carbonyl]phenyl]-1H-benzimidazole-5-sulfonamide; or

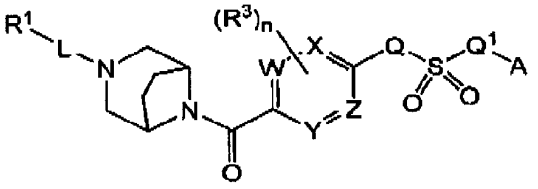
2,3-dihydro-2-oxo-N-[4-[[4-(2-pyridinyl)-1-piperazinyl]carbonyl]phenyl]-1H-benzimidazole-5-sulfonamide.

2. The compound of claim 1, wherein In certain embodiments of a compound of formula (I) or a pharmaceutically acceptable salt thereof p is 1 or 2.

3. The compound of claim 2, wherein p is 2 and the compound has the formula Ia:



(Ia), or formula Ib:



(Ib), wherein $R^1$, L, $R^3$, W, X, Y, Z, Q, $Q^1$, A, and n are as defined in claim 1.

4. The compound of claim 2, wherein:

p is 1 or 2; and

each $R^4$ is independently selected from alkyl, phenyl, (*S*)-alkyl,

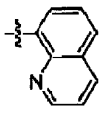
(*R*)-alkyl, (*S*)-phenyl, and (*R*)-phenyl.

5. The compound of claim 4, wherein:

g is 1;

h is 1; and

each $R^4$ is independently selected from methyl, (*S*)-methyl, (*R*)-methyl, ethyl, (*S*)-ethyl, (*R*)-ethyl, isopropyl, (*S*)-isopropyl, (*R*)-isopropyl, phenyl, (*S*)-phenyl, and (*R*)-phenyl.

6. The compound of any one of claims 1-5, wherein A is  .

7. The compound of any one of claims 1-6, wherein W, X, Y, Z and the carbons to which they are attached form a phenyl ring.

8. The compound of any one of claims 1-7, wherein:

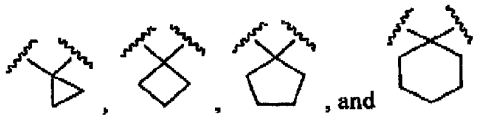
n is 1; and

$R^3$ is selected from fluoro, chlororo, methyl, ethyl, $CF_3$, methoxy, and $OCF_3$.

9. The compound of any one of claims 1-8, wherein:

Q is NH.

10. The compound of any one of claims 1-9, wherein L is selected from a bond, -C(O)-, -OC(O)-, $-CH_2$-OC(O)-, $-(CH_2)_2$-OC(O)-, $-C(CH_3)_2$-C(O)-, $-CH_2$-, $-(CH_2)_2$-, $-(CH_2)_3$-, $-CH(CH_3)$-, $-CH(CF_3)$-, $-C(CH_3)_2$-, -CHD-, $-CD_2$-,

 , and .

**Application No.: PCT/US2011/067752** **Docket No.: C2081-7035WO**

11. The compound of any one of claims 1-10, wherein $R^1$ is selected from methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 1,2,3-thiadiazol-5-yl, 1,2,3-thiadiazol-4-yl, thiazol-4-yl, thiazol-5-yl, 1H-imidazol-4-yl, 1H-imidazol-2-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, pyrazin-2-yl, oxazol-4-yl, isoxazol-5-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydro-2H-pyran-4-yl, tetrahydro-2H-pyran-3-yl, and tetrahydro-2H-pyran-2-yl.

12. The compound of claim 1, wherein the compound is selected from a compound of Tables 1-2 and 3-4.

13. The compound of claim 12, wherein the compound is selected from any one of Compounds 108, 110, 111, 112, 113, 114, 118, 119, 120, 122, 123, 125, 128, 129, 130, 131, 132, 133, 135, 137, 140, 142, 143, 144, 145, 147, 148, 149, 150, 151, 152, 155, 160, 161, 163, 165, 167, 183, 186, 189, 190, 194, 196, 199, 200, 203, 206, 211, 212, 213, 216, 217, 220, 221, 222, and 223.

14. A pharmaceutical composition comprising a compound of a claim 1, and a pharmaceutically acceptable carrier.

15. A method of activating PKM2 activity in a subject in need thereof, comprising the step of administering to the subject a pharmaceutical composition of claim 14.

16. A method of treating a cancer associated with reduced PKM2 activity in a subject in need thereof, the method comprising administering to a subject a pharmaceutical composition of claim 14.

17. A composition comprising a compound of a claim 1, and a pharmaceutically acceptable carrier for use in treating a cancer associated with reduced PKM2 activity.

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
McCarty, Catherine M.
Lando & Anastasi, LLP
One Main Street
Eleventh Floor
Cambridge, MA 02142
ETATS-UNIS D'AMERIQUE

# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

| | |
|---|---|
| | Date of mailing *(day/month/year)* 5 March 2012 (05-03-2012) |
| Applicant's or agent's file reference C2081-7035WO | **FOR FURTHER ACTION** See paragraphs 1 and 4 below |
| International application No. PCT/US2011/067752 | International filing date *(day/month/year)* 29 December 2011 (29-12-2011) |
| Applicant AGIOS PHARMACEUTICALS, INC. | |

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   **Filing of amendments and statement under Article 19:**
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   **When?** The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   **Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   **For more detailed instructions, see *PCT Applicant's Guide*,** International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

| Name and mailing address of the International Searching Authority | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk<br>Tel. (+31-70) 340-2040<br>Fax: (+31-70) 340-3016 | STARK, Saskia<br>Tel: +49 (0)89 2399-4764 |

Form PCT/ISA/220 (July 2010)

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | **FOR FURTHER ACTION** | see Form PCT/ISA/220 as well as, where applicable, item 5 below. |
|---|---|---|
| C2081-7035WO | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/US2011/067752 | 29/12/2011 | 29/12/2010 |
| Applicant | | |
| AGIOS PHARMACEUTICALS, INC. | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/067752

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/496 A61P35/00
ADD.

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)
A61K

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 practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2003/207882 A1 (STOCKER ANDREW [GB] ET AL) 6 November 2003 (2003-11-06)<br>page 8 - paragraph 168 | 1,7,10, 11,14 |
| X | WO 2007/023186 A1 (APPLIED RESEARCH SYSTEMS [NL]; GAILLARD PASCALE [FR]; QUATTROPANI ANNA)<br>1 March 2007 (2007-03-01)<br>page 135; example 130<br>page 145; example 146<br>claims 15, 17,21 | 1-17 |
| X,P | WO 2011/002817 A1 (AGIOS PHARMACEUTICALS INC [US]; SAUNDERS JEFFREY O [US]; SALITURO FRAN) 6 January 2011 (2011-01-06)<br>page 2, paragraph 3<br>claims 1-30<br>figure 1 | 1-17 |

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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 document 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 |
|---|---|
| 22 February 2012 | 05/03/2012 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Terenzi, Carla |

1

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/067752

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 2010/105243 A1 (AGIOS PHARMACEUTICALS INC [US]; DANG LENNY [US]; FANTIN VALERIA [US];) 16 September 2010 (2010-09-16) the whole document<br>----- | 1-17 |

1

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/067752

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 2003207882 A1 | 06-11-2003 | NONE | |
| WO 2007023186 A1 | 01-03-2007 | AU 2006283846 A1 | 01-03-2007 |
| | | CA 2618479 A1 | 01-03-2007 |
| | | EA 200800668 A1 | 29-08-2008 |
| | | EP 2351745 A1 | 03-08-2011 |
| | | JP 2009506015 A | 12-02-2009 |
| | | KR 20080049767 A | 04-06-2008 |
| | | US 2009082356 A1 | 26-03-2009 |
| | | US 2011312960 A1 | 22-12-2011 |
| | | US 2011319410 A1 | 29-12-2011 |
| | | WO 2007023186 A1 | 01-03-2007 |
| WO 2011002817 A1 | 06-01-2011 | AR 077292 A1 | 17-08-2011 |
| | | TW 201103913 A | 01-02-2011 |
| | | US 2010331307 A1 | 30-12-2010 |
| | | WO 2011002817 A1 | 06-01-2011 |
| WO 2010105243 A1 | 16-09-2010 | AU 2010223919 A1 | 06-10-2011 |
| | | CA 2755394 A1 | 16-09-2010 |
| | | EP 2406389 A1 | 18-01-2012 |
| | | WO 2010105243 A1 | 16-09-2010 |

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 13939519 |
| **Filing Date:** | 11-Jul-2013 |
| **Title of Invention:** | METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS |
| **First Named Inventor/Applicant Name:** | Leonard Luan C. Dang |
| **Filer:** | Asimini T. Georges Evangelinos/Timothy Vogel |
| **Attorney Docket Number:** | C2081-701320 |

Filed as Large Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| Submission- Information Disclosure Stmt | 1806 | 1 | 180 | 180 |
| | | **Total in USD ($)** | | **180** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 26934881 |
| **Application Number:** | 13939519 |
| **International Application Number:** | |
| **Confirmation Number:** | 2110 |
| **Title of Invention:** | METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS |
| **First Named Inventor/Applicant Name:** | Leonard Luan C. Dang |
| **Customer Number:** | 94970 |
| **Filer:** | Asimini T. Georges Evangelinos |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | C2081-701320 |
| **Receipt Date:** | 15-SEP-2016 |
| **Filing Date:** | 11-JUL-2013 |
| **Time Stamp:** | 14:13:14 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $180 |
| RAM confirmation Number | 486 |
| Deposit Account | 502762 |
| Authorized User | Georges Evangelinos, Asimina |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees)<br>Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees) | |

Charge any Additional Fees required under 37 CFR 1.19 (Document supply fees)

Charge any Additional Fees required under 37 CFR 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Amendment/Req. Reconsideration-After Non-Final Reject | Amendment_OA_of_6_16_2016.pdf | 46709<br>6bb61d8f832a691d280fee0c95de4293363c006e | no | 7 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Transmittal Letter | Information_Disclosure_Statement.pdf | 26604<br>bab3703ad7911da98f40bd2e248aa13569f634fb | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Information Disclosure Statement (IDS) Form (SB08) | Information_Disclosure_Statement_Fillable_PDF.pdf | 1037547<br>dea906e5912f3e874438baa6f28ddff4b9680bcb | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Foreign Reference | CN101296909A.pdf | 6582331<br>ba41009d41c85bc089b37ebde5cce9603191b4ab | no | 154 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Foreign Reference | Translation_of_CN101296909A.pdf | 66371<br>1daa082734fc9fc695304a04d27600d2826151ef | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Foreign Reference | EP22958A1.pdf | 1286580<br>e552e77e8dce543c91acb5b1d1e74508c58bdf4a | no | 52 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 7 | Foreign Reference | WO96030343A1.pdf | 8560017<br>d366a7423358b08408f6e527b59623dd0b4b38ca | no | 294 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 8 | Foreign Reference | WO97044322A1.pdf | 1096929<br>dfa9274571da7f4a81616f1e0baa0dd50f521338 | no | 25 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 9 | Foreign Reference | WO2001019788A2.pdf | 7173099<br>20b0601920b813606eb4771799b3133e9cdda087 | no | 224 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 10 | Foreign Reference | WO2001019798A2.pdf | 7760656<br>174afe9f0471df68cadb7d01f157bebe159c85d2 | no | 314 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 11 | Foreign Reference | WO2001064642A2.pdf | 8955198<br>03f5d527e53978bd8d63f41969c9bd8bc4b7d781 | no | 306 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 12 | Foreign Reference | WO2001064643A2.pdf | 9898599<br>b1b082928e5b4844101f01b96a85665551ce9dad | no | 322 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 13 | Foreign Reference | WO2002100822A1.pdf | 4592158<br>4198cb890e3c4a3a71b044ef8d94116caa996a1f | no | 131 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 14 | Foreign Reference | WO2004089470A2.pdf | 11469775<br>6400059418bd4b1e49a105ed6c39544c6d5b9e3c | no | 236 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 15 | Foreign Reference | WO2005120474A2.pdf | 1393369<br>56996f2da72a76b275145d80196a47d4d0ca5118 | no | 25 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 16 | Foreign Reference | WO2006034341A2.pdf | 2993679<br>2a73b1faf62c9b1199c5bc8202043f606eac433d | no | 53 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 17 | Foreign Reference | WO2007003934A2.pdf | 10733114<br>2a7d01c36143cfe0d7f4c21fbf54a9dfaadb5a6d | no | 266 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 18 | Foreign Reference | WO2008052190A2.pdf | 12778594<br>c1f2e77a070a4d07856925dedf967e9c188409ce | no | 141 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 19 | Foreign Reference | WO2008073670A2.pdf | 4166664<br>37826427255eb6cc6ad1b5730f572110e4eaed38 | no | 108 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 20 | Foreign Reference | WO2009126863A2.pdf | 8168420<br>9946faeaf20934a2fe5da22813fef6e78d39bf72 | no | 263 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 21 | Foreign Reference | WO2010129596A1.pdf | 2862839<br>3e1289b6bfbedd51c8cf05b821533496870<br>17159 | no | 78 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 22 | Foreign Reference | WO2010130638A1.pdf | 5433371<br>d0953ca74fe8e7876a4ca3ecac8be0d44841<br>a627 | no | 111 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 23 | Foreign Reference | WO2011032169A2.pdf | 8762157<br>7380155c9b418e7aa82161ffd018e1d9462<br>226c6 | no | 173 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 24 | Foreign Reference | WO2011047432A1.pdf | 6313677<br>1183a40434f974ab6293a69b78f38219655<br>68c77 | no | 162 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 25 | Foreign Reference | WO2012092442A1.pdf | 5401011<br>ac8ff4acb3e807e507791cf97b96e967e151<br>9636 | no | 165 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 26 | Foreign Reference | WO2012151452A1.pdf | 5873246<br>7375f2b4446aa226acf880c3e492470c85dd<br>9a00 | no | 181 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 27 | Foreign Reference | WO9728128A1.pdf | 5470851<br>e10e06f2b3f146b14b1ebf6b5a23998abe1<br>4b467 | no | 153 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 28 | Foreign Reference | WO9932463A1.pdf | 4075686<br>105eeac6383dfbd318b58614fdbad86cff13c928 | no | 107 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 29 | Non Patent Literature | C2081-7035WO_PCT_IPEA__409_APRIL_11_2013.PDF | 644488<br>11e416e0cc3f51debb43d1b5caa3c9d334c4e1e9 | no | 14 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 30 | Non Patent Literature | C2081-7035WO_ISR_PCTUS2011067752_Dated_030512.pdf | 224347<br>2a82baf59c738dfde66a34771a94027f22ec608b | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 31 | Non Patent Literature | 16-05-25_Cited_Reference_11_C2081-7047JP_F1-13N96BVR.PDF | 33926<br>ae52d8df0fce9fa5b5fec639357b462ac1376e99 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 32 | Non Patent Literature | 16-05-25_Cited_Reference_10_C2081-7047JP_F1-13N96BVR.PDF | 33749<br>018ef60d571ea02f90ef82b92c4dd5ebf372f142 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 33 | Non Patent Literature | 16-05-25_Cited_Reference_7_C2081-7047JP_F1-13N96BVR.PDF | 35967<br>98d607c80e0911fd3470cc0be96f15cd84ba47d9 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 34 | Non Patent Literature | 16-05-25_Cited_Reference_12_C2081-7047JP_F1-13N96BVR.PDF | 36956<br>50996bc0012c07e7105102b1d5b1107adbe00abb | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 35 | Non Patent Literature | 16-05-25_Cited_Reference_8_C 2081-7047JP_F1-13N96BVR. PDF | 34590<br>98478db18fa6e753275ab191c80c63bea4e b623f | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 36 | Non Patent Literature | 16-05-25_Cited_Reference_9_C 2081-7047JP_F1-13N96BVR. PDF | 33745<br>a0fa9866a8fc8f90cc3e6f6e1cbb8856290ff2 f6 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 37 | Non Patent Literature | STN5.pdf | 54429<br>ff985d1ecdb2658b5a9461d6d32147652ae 51b71 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 38 | Non Patent Literature | STN4.pdf | 60651<br>947f074530fecdafbda9c0bc101390c86bb4 beca | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 39 | Non Patent Literature | STN3.pdf | 56541<br>13a2ed3a99aeb382d851982bcfcc6e3f8a00 ea0a | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 40 | Non Patent Literature | STN2.pdf | 57416<br>eec737d1a21e523fbbdbbaf070827a6bff5a 4461 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 41 | Non Patent Literature | STN1.pdf | 58269<br>eb5fccdd1674f2411e358e292a29e72bff17 d825 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 42 | Non Patent Literature | STN20.pdf | 63580<br>4515c892ca5b267f6797c823621d390aaa8a93d8 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 43 | Non Patent Literature | STN_19.pdf | 66037<br>2cfd203e631f3a0e3349d835c2cfca2a03ac7246 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 44 | Non Patent Literature | STn18.pdf | 63157<br>7f1060626489c7f10ff0f0b6c56c78a9d10939c3 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 45 | Non Patent Literature | STN17.pdf | 67003<br>17c0bfed9f20dbf2fb5cbca48deb7c5659312856 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 46 | Non Patent Literature | STN16.pdf | 67400<br>48952deea021e8b1548f4a8568587e7aa8f87143 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 47 | Non Patent Literature | STN15.pdf | 65254<br>fddf7b8d86a4bd0a8e772f1287a71360cbbb7806 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 48 | Non Patent Literature | STN14.pdf | 59990<br>1f716ea14f2d965c893fc452d1b6876db0a4d151 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 49 | Non Patent Literature | STN13.pdf | 58307<br>7543daba9c14d2a22f68621b0b62e7d6ef2e501f | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 50 | Non Patent Literature | STN12.pdf | 58696<br>9a1ad2062bf0e420d75754e4d7232148bea42472 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 51 | Non Patent Literature | STN11.pdf | 59839<br>269039b45f9a47a9c3cd52a4f5dfcca55515df85 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 52 | Non Patent Literature | STN10.pdf | 58646<br>df028c38235fe6b8150ebcc39eab46254134a93d | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 53 | Non Patent Literature | STN9.pdf | 59041<br>e57baee3a626b2ce66ad86aeefc06762fbac7c49 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 54 | Non Patent Literature | STN8.pdf | 57914<br>32da9f4c785fcddb69e5151b7a2b6ed88f34ef23 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 55 | Non Patent Literature | STN7.pdf | 58625<br>4ccaa5ade14f7d4b099d09ca00bbebf95ac77924 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 56 | Non Patent Literature | STN6.pdf | 57030<br>0efb5638cc4802b0569919e05e8bc4a609f7afe6 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 57 | Non Patent Literature | NPL_-_Lutker_et_al_Crystal_Polymorphism.pdf | 1058223<br>684928455ae8d43c2c124d7457a70c57f9faebdb | no | 17 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 58 | Non Patent Literature | NPL_-_Rao_et_al_Polymorphism_in_Drugs.pdf | 587977<br>1b4a6f6e80c5328199fb421c1685cee1154552a3 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 59 | Non Patent Literature | NPL_-_Docoslis_et_al_Characterization_of_the_Distribution.pdf | 950239<br>854924b1e3bbd0fe4b4d056a0fbda58074f74e7f | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 60 | Fee Worksheet (SB06) | fee-info.pdf | 30605<br>63260e29288855ef22bf06e838ad8448a9d4d432 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 157891888 | | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


| PATENT APPLICATION FEE DETERMINATION RECORD<br>Substitute for Form PTO-875 | Application or Docket Number<br>13/939,519 | Filing Date<br>07/11/2013 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY**: ☒ LARGE ☐ SMALL ☐ MICRO

## APPLICATION AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | RATE ($) | FEE ($) |
|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | |
| ☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | |

## APPLICATION AS AMENDED – PART II

| AMENDMENT | 09/15/2016 | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|
| | Total (37 CFR 1.16(i)) | * 14 | Minus | ** 20 | = 0 | X $80 = | 0 |
| | Independent (37 CFR 1.16(h)) | * 1 | Minus | ***3 | = 0 | X $420 = | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | |
| | | | | | | TOTAL ADD'L FEE | **0** |

| AMENDMENT | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|
| | Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | |
| | | | | | | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/MOLIKI MAY/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 13/939,519 | 07/11/2013 | Leonard Luan C. Dang | C2081-701320 | 2110 |

94970 7590 06/16/2016

LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

| EXAMINER |
|---|
| HIXSON, CHRISTOPHER |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1797 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 06/16/2016 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DOCKETING@LALaw.COM
pair_agios@firsttofile.com
CKent@LALaw.com

| Examiner-Initiated Interview Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 13/939,519 | DANG ET AL. | |
| | Examiner | Art Unit | |
| | Christopher A. Hixson | 1797 | |

All participants (applicant, applicant's representative, PTO personnel):

(1) *Christopher A. Hixson*. (3)_____.

(2) *Asimina T. Georges Evangelinos*. (4)_____.

Date of Interview: *27 May 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☒101 ☒112 ☒102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *93*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

*The examiner indicated that he considered that a claim which incorporated claims 93, 102, 103, (each reciting particular mutations associated with a cancer) and 106 (reciting a non-conventional, non-obvious analysis method) would likely be patentable because it would not be rejectable over 101 or 112. The applicants declined his offer to make an examiner's amendment*.

**Applicant recordation instructions**: It is not necessary for applicant to provide a separate record of the substance of interview.

**Examiner recordation instructions**: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

| /Christopher A. Hixson/<br>Primary Examiner, Art Unit 1797 | |
|---|---|

| Office Action Summary | Application No. 13/939,519 | Applicant(s) DANG ET AL. | |
|---|---|---|---|
| | Examiner Christopher A. Hixson | Art Unit 1797 | AIA (First Inventor to File) Status No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *2/11/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5)☒ Claim(s) *93-95 and 97-106* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *93-95 and 97-106* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *2/11/2016*.

3) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *27 May 2016* .

4) ☐ Other: _____.

1. The present application is being examined under the pre-AIA first to invent provisions.

## DETAILED ACTION

2. The amendment dated 11 February 2016 is acknowledged. Claims 1-92 and 96 are cancelled. Claims 100-106 are newly added. Therefore claims 93-95 and 97-106 are pending and considered on the merits below.

3. No rejections over 35 USC 112 or 101 are withdrawn, as the amendment merely changes the precise grounds upon which the claims can be rejected. The rejection over prior art, however, is modified to articulate a different ground of rejection and for this reason, this action is not made final.

### *Priority*

4. Because no support for the correlation between mutants of IDH1 and IDH2 and 2HG neoactivity, required by all claims as filed, can be found in earlier priority documents, priority for claims including such a requirement are traced to US 61/173,518, filed 28 April 2009.

### *Claim Interpretation/Rejections - 35 USC § 112*

5. The examiner notes that the word "neoactivity" is defined by the applicant's specification. Provisional application 61/160,253 is incorporated by reference into the

present disclosure in [0001]. On p.3 of the '253 application, neoactivity is said to mean an activity which arises as a result of a mutation of an enzyme. In [0018] of the present specification, 2HG neoactivity is defined to "refer[] to the ability to convert alpha ketoglutarate to 2-hydroxyglutarate (sometimes referred to herein as 2HG)" because of the mutation of an enzyme.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. **Claims 93-95, 97-99 and 104-106** are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

Regarding claim 93, the claim requires detection of a particular substance (2HG) in a particular population (those people not having 2-hydroxyglutaric aciduria) as a means of evaluating the subject for “the presence or susceptibility" to a cancer.

While the specification discusses particular cancers having the aforementioned qualities (elevated 2HG in the particular population is correlated with specific mutations causing a specific type of cancer), this lies claim to diagnosing all cancers having this quality, even those potentially not discovered by the applicant.

When one makes a claim to a genus, one must describe a sufficient number of representative species to support such a claim. The required number of such species varies on a case-by-case basis. (see MPEP 2163). Here, the applicants have sufficient support for the claims not rejected on this basis, but lack support for claims having a broader scope regarding the cancer limitation because as noted before, the molecular biology of cancer is generally unpredictable, and the evidence provided does not support the broader claim in view of this unpredictability.

Dependent claims, because they are said to predict the same broad category of cancers (or an also impermissibly broad genus of cancer) are rejected over the same rationale.

8. Claims **93-95, 97-99 and 104-106** are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

With respect to the issue of enablement, attention is directed to the factors to be considered as laid out in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (see MPEP 2164).

***a. The breadth of the claims and the nature of the invention***

Regarding claim 93, one is to evaluate a subject for cancer (or cancer susceptibility) based on (at least) the result of an analysis the presence, distribution, or level of 2HG in a subject who does not have 2-HG aciduria.

In each of these claims, practically the only manipulative step required is a test for 2GH, the rest being mental or computational steps. As such, the claims are construed quite broadly.

***b. The state of the prior art***

The examiner notes that the prior art indicates the elevated 2HG can occur in conditions unrelated to that which the present invention concerns itself. For example, the Genetics Home Reference Website L2HGDH entry teaches that 2HG can become elevated in a different disorder unrelated to IDH (namely, an error in L-2-hydroxyglutarate dehydrogenase allows excess 2HG to accumulate). So the examiner concludes that elevated 2HG does not necessarily correlate with IDH 2HG neoactivity and especially not to cancer in general. Therefore, when the analyzing step includes simply determining the presence or level of 2HG, the examiner does not know how this

can be distinguished between the correlation the applicant recites or some other known (or even unknown) correlation.

***c. The level of one of ordinary skill***

The skill is at the postgraduate level.

***d. The level of predictability in the art***

The examiner officially noted that molecular biology is a generally unpredictable field. Since this went unchallenged, it is not taken as admitted.

***e. The amount of direction provided by the inventor and the existence of working examples***

The examiner sees no guidance or working examples demonstrating enablement provided by the application on the issue he raises here.

***f. The quantity of experimentation needed***

Based on the analysis above, the examiner deems that an undue amount of experimentation would be required to practice the invention, as no guidance is provided to surmount the issue either in the art or by the applicant's disclosure.

## *Claim Rejections - 35 USC § 101*

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

**Claims 93-95 and 97-105** are rejected under 35 U.S.C. 101 because the claimed invention is directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more.

Claim(s) 93-105 is/are directed to a method which recites both an abstract idea and a natural law. Claim 93 is directed to the correlation of 2HG presence, distribution, or level in a particular type of subject and the “presence or susceptibility to cancer" in a step in which the patient is said be “evaluated” (the correlation is a natural law, the implied diagnosis is an abstract idea).

The claim(s) does/do not include additional elements that are sufficient to amount to significantly more than the judicial exception.

Regarding claim 93, the analysis step is recited quite generically, and because it is a necessary step to gather information for the abstract idea and is otherwise necessary to make much use of the natural correlation, it cannot be said to add anything significantly more to the claim.

Dependent claims fail to add anything significantly more, and many simply raise new issues of subject matter eligibility.

Claims such as 94, 95, 100-103, and 105 simply appear to refine the natural law and/or the abstract idea claimed and therefore cannot be said to add something “significantly more."

Claims such as claims 97-99 and 104 for example recite particulars of the analysis step, but do so in ways which remain entirely conventional. In a previous action, the examiner officially noted that MRI has been used to detect particular

molecules in a subject (see the molecular MRI field), but this went unchallenged and so is taken as admitted. Additionally, the examiner cited to Sosnovik et al. (Curr Op Biotech 2007), pp.7-8, and this was further evidence that such is to be considered conventional by the examiner. That one must analyze "a tissue, product, or bodily fluid of the subject" scarcely limits the analysis step in any meaningful way. The examiner does not see that these limitations add something significantly more as is required when taken individually or when considering the claim as a whole.

***Discussion of Prior Art***

10. Above, the examiner indicated his conclusion that the correlation between IDH1 and/or IDH2 mutation and 2HG neoactivity was first discovered by the applicants and first published in a work which is not prior art for the present application. As evidence for his conclusion, the examiner refers to the following references. First, Lou (Nature 2009) writes in an article that this correlation was first published in a paper written by the applicants (p.1, the Agios study), after the priority date established by the examiner, see Dang et al. (Nature 2009). Secondly, Aghili et al. (J. Neurooncology 2009), in a work published a few months before the priority date indicates that the metabolic pathway and enzymatic defect in a disease which was characterized by elevated 2HG (and is otherwise similar in nature to what is described by the applicants in their disclosure) was not well known (p.233). Given this evidence, and no other evidence demonstrating that this correlation was known before the priority date, the examiner

finds no prior art rejection possible for claims 100-103 which requires knowledge of this correlation.

***Claim Rejections - 35 USC § 102***

11. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

12. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. **Claims 93-95, 99, and 105** are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Struys et al. (Clinical Chemistry 2004) as evidenced by Aghili et al. (J. Neurooncol 2009).

Regarding claims 93 and 99, Struys teaches that he analyzed the subject for the presence, distribution or level of 2HG in a case where the subject does not have or is not diagnosed with 2-hydroxyglutaric aciduria (abstract, where this is done to test for 2-HGA, where some patients tested will not have the disease, implicitly; p.1395, col. 1, where sample tested is urine). That one simultaneously then evaluates for the susceptibility of cancer comes from the fact that the test above distinguishes healthy

people from those with L-, L/D-, or D-2-hydroxyglutaric aciduria, while L-2-hydroxyglutaric aciduria has been associated with a particular type of cancer (abstract).

Regarding claims 94, 95, and 105, the cancer is an astrocytic tumor and a glioblastoma, or a glioma (see Aghili; p.235 and Fig. 2, gilal tissue).

***Response to Arguments***

14. Applicant's arguments filed 11 February 2016 have been fully considered but they are not persuasive.

Regarding the rejection over written description, the applicants argue that their amendment moots the rejection. The examiner disagrees, and points them to the detailed rejection above for his rationale.

Regarding the rejection over enablement, the applicants argue that their amendment moots the rejection. The examiner disagrees, and points them to the detailed rejection above for his rationale.

Regarding the rejection over 35 USC 101, the applicants assert that their claims “recite something significantly different than the judicial exceptions, and therefore are directed toward patent eligible subject matter." In particular, they claim that their claim is limited to a "particular practical application." As evidence they indicate that the analysis step of claim 93 requires "a practical application, such as spectroscopic analysis." This argument does not affect the examiner’s determination above, because it is not relevant to the required analysis. The examiner above identified a natural law and/or an abstract idea, and then indicated that certain other steps did not amount to

significantly more because they were conventional. The “analysis step" of claim 93 might contain within its scope examples of analysis which are not conventional, and which then render the claim into a “particular practical application,” however, the claim at present does not. Because the applicant’s arguments fail to demonstrate that the claims are directed to patent-eligible subject matter, the claims remain rejected over this ground.

Regarding the rejection over prior art, the examiner has entered a new rejection.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher A. Hixson whose telephone number is (571)270-5027. The examiner can normally be reached on M-F 9 am - 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Lyle Alexander can be reached on (571)272-1254. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christopher A. Hixson/
Primary Examiner, Art Unit 1797

| Examiner-Initiated Interview Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 13/939,519 | DANG ET AL. | |
| | Examiner | Art Unit | |
| | Christopher A. Hixson | 1797 | |

All participants (applicant, applicant's representative, PTO personnel):

(1) *Christopher A. Hixson*. (3)_____.

(2) *Asimina T. Georges Evangelinos*. (4)_____.

Date of Interview: *27 May 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☒101 ☒112 ☒102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *93*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

*The examiner indicated that he considered that a claim which incorporated claims 93, 102, 103, (each reciting particular mutations associated with a cancer) and 106 (reciting a non-conventional, non-obvious analysis method) would likely be patentable because it would not be rejectable over 101 or 112. The applicants declined his offer to make an examiner's amendment*.

**Applicant recordation instructions**: It is not necessary for applicant to provide a separate record of the substance of interview.

**Examiner recordation instructions**: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

| /Christopher A. Hixson/<br>Primary Examiner, Art Unit 1797 | |
|---|---|

| Notice of References Cited | Application/Control No. 13/939,519 | Applicant(s)/Patent Under Reexamination DANG ET AL. | |
|---|---|---|---|
| | Examiner Christopher A. Hixson | Art Unit 1797 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | CPC Classification | US Classification |
|---|---|---|---|---|---|---|
| | A | US- | | | | |
| | B | US- | | | | |
| | C | US- | | | | |
| | D | US- | | | | |
| | E | US- | | | | |
| | F | US- | | | | |
| | G | US- | | | | |
| | H | US- | | | | |
| | I | US- | | | | |
| | J | US- | | | | |
| | K | US- | | | | |
| | L | US- | | | | |
| | M | US- | | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | CPC Classification |
|---|---|---|---|---|---|---|
| | N | | | | | |
| | O | | | | | |
| | P | | | | | |
| | Q | | | | | |
| | R | | | | | |
| | S | | | | | |
| | T | | | | | |

**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | Struys, Eduard A. et al. "Measurement of Urinary D- and L-2-Hydroxyglutarate Enantiomers by Stable-Isotope-Dilution Liquid Chromatography–Tandem Mass Spectrometry after Derivatization with Diacetyl-L-Tartaric Anhydride." Clinical Chemistry (2004) 50 1391-1395. |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | 1797 |
| Examiner Name | C. Hixson |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | | | | | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 20100273808 | A1 | 2010-10-28 | Armitage et al. | |
| | 2 | 20110086088 | A1 | 2011-04-14 | Berry | |
| | 3 | 20120121515 | A1 | 2012-05-17 | Dang et al. | |
| | 4 | 20120129865 | A1 | 2012-05-24 | WANG et al. | |
| | 5 | 20120238576 | A1 | 2012-09-20 | Tao et al. | |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | 1797 |
| Examiner Name | C. Hixson |
| Attorney Docket Number | C2081-701320 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 6 | 20130109643 | A1 | 2013-05-02 | Riggins et al. | |
| | 7 | 20130184222 | A1 | 2013-07-18 | Popovici-Muller et al. | |
| | 8 | 20130190249 | A1 | 2013-07-25 | Lemieux et al. | |
| | 9 | 20140187435 | A1 | 2014-07-03 | Dang et al. | |
| | 10 | 20150018328 | A1 | 2015-01-15 | Konteatis et al. | |
| | 11 | 20150031627 | A1 | 2015-01-29 | Lemieux et al. | |
| | 12 | 20150044716 | A1 | 2015-02-12 | Balss et al. | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2014015422 | WO | A1 | 2014-01-30 | Ontario Inst For Cancer Res | | |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

EFS Web 2.1.17

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | 1797 |
| Examiner Name | C. Hixson |
| Attorney Docket Number | C2081-701320 |

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|
| | 1 | International Preliminary Report on Patentability for International Application No. PCT/CN2012/000841 dated September 10, 2012 | |
| | 2 | International Preliminary Report on Patentability for International Application No. PCT/CN2012/077096 dated September 17, 2012 | |
| | 3 | International Search Report and Written Opinion for Internatinal Application No. PCT/US2013/064601 dated February 24, 2014 | |
| | 4 | International Search Report and Written Opinion for International Application No. PCT/US15/020349 dated June 15, 2015 | |
| | 5 | International Search Report and Written Opinion for International Application No. PCT/US2015/020346 dated June 18, 2015 | |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | /Christopher Adam Hixson/ | Date Considered | 06/02/2016 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | 1797 |
| Examiner Name | C. Hixson |
| Attorney Docket Number | C2081-701320 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Asimina T. Georges Evangelinos/ | Date (YYYY-MM-DD) | 2016-02-11 |
| Name/Print | Asimina T. Georges Evangelinos | Registration Number | 66888 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

/Christopher Adam Hixson/ 06/02/2016

EFS Web 2.1.17 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | **Examiner** | **Art Unit** |
| | CHRISTOPHER A HIXSON | 1797 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/04/2015 | 06/02/2016 | | | | | | | |
| | 1 | - | - | | | | | | | |
| | 2 | - | - | | | | | | | |
| | 3 | - | - | | | | | | | |
| | 4 | - | - | | | | | | | |
| | 5 | - | - | | | | | | | |
| | 6 | - | - | | | | | | | |
| | 7 | - | - | | | | | | | |
| | 8 | - | - | | | | | | | |
| | 9 | - | - | | | | | | | |
| | 10 | - | - | | | | | | | |
| | 11 | - | - | | | | | | | |
| | 12 | - | - | | | | | | | |
| | 13 | - | - | | | | | | | |
| | 14 | - | - | | | | | | | |
| | 15 | - | - | | | | | | | |
| | 16 | - | - | | | | | | | |
| | 17 | - | - | | | | | | | |
| | 18 | - | - | | | | | | | |
| | 19 | - | - | | | | | | | |
| | 20 | - | - | | | | | | | |
| | 21 | - | - | | | | | | | |
| | 22 | - | - | | | | | | | |
| | 23 | - | - | | | | | | | |
| | 24 | - | - | | | | | | | |
| | 25 | - | - | | | | | | | |
| | 26 | - | - | | | | | | | |
| | 27 | - | - | | | | | | | |
| | 28 | - | - | | | | | | | |
| | 29 | - | - | | | | | | | |
| | 30 | - | - | | | | | | | |
| | 31 | - | - | | | | | | | |
| | 32 | - | - | | | | | | | |
| | 33 | - | - | | | | | | | |
| | 34 | - | - | | | | | | | |
| | 35 | - | - | | | | | | | |
| | 36 | - | - | | | | | | | |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | **Examiner** | **Art Unit** |
| | CHRISTOPHER A HIXSON | 1797 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/04/2015 | 06/02/2016 | | | | | | | |
| | 37 | - | - | | | | | | | |
| | 38 | - | - | | | | | | | |
| | 39 | - | - | | | | | | | |
| | 40 | - | - | | | | | | | |
| | 41 | ✓ | - | | | | | | | |
| | 42 | ✓ | - | | | | | | | |
| | 43 | ✓ | - | | | | | | | |
| | 44 | ✓ | - | | | | | | | |
| | 45 | ✓ | - | | | | | | | |
| | 46 | ✓ | - | | | | | | | |
| | 47 | ✓ | - | | | | | | | |
| | 48 | ✓ | - | | | | | | | |
| | 49 | ✓ | - | | | | | | | |
| | 50 | ✓ | - | | | | | | | |
| | 51 | ✓ | - | | | | | | | |
| | 52 | ✓ | - | | | | | | | |
| | 53 | ✓ | - | | | | | | | |
| | 54 | ✓ | - | | | | | | | |
| | 55 | ✓ | - | | | | | | | |
| | 56 | ✓ | - | | | | | | | |
| | 57 | N | - | | | | | | | |
| | 58 | N | - | | | | | | | |
| | 59 | N | - | | | | | | | |
| | 60 | N | - | | | | | | | |
| | 61 | N | - | | | | | | | |
| | 62 | N | - | | | | | | | |
| | 63 | ✓ | - | | | | | | | |
| | 64 | ✓ | - | | | | | | | |
| | 65 | ✓ | - | | | | | | | |
| | 66 | N | - | | | | | | | |
| | 67 | N | - | | | | | | | |
| | 68 | N | - | | | | | | | |
| | 69 | N | - | | | | | | | |
| | 70 | N | - | | | | | | | |
| | 71 | N | - | | | | | | | |
| | 72 | N | - | | | | | | | |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | **Examiner** | **Art Unit** |
| | CHRISTOPHER A HIXSON | 1797 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/04/2015 | 06/02/2016 | | | | | | | |
| | 73 | N | - | | | | | | | |
| | 74 | N | - | | | | | | | |
| | 75 | N | - | | | | | | | |
| | 76 | N | - | | | | | | | |
| | 77 | N | - | | | | | | | |
| | 78 | N | - | | | | | | | |
| | 79 | N | - | | | | | | | |
| | 80 | ✓ | - | | | | | | | |
| | 81 | ✓ | - | | | | | | | |
| | 82 | ✓ | - | | | | | | | |
| | 83 | ✓ | - | | | | | | | |
| | 84 | ✓ | - | | | | | | | |
| | 85 | ✓ | - | | | | | | | |
| | 86 | ✓ | - | | | | | | | |
| | 87 | ✓ | - | | | | | | | |
| | 88 | ✓ | - | | | | | | | |
| | 89 | ✓ | - | | | | | | | |
| | 90 | ✓ | - | | | | | | | |
| | 91 | ✓ | - | | | | | | | |
| | 92 | ✓ | - | | | | | | | |
| | 93 | ✓ | ✓ | | | | | | | |
| | 94 | ✓ | ✓ | | | | | | | |
| | 95 | ✓ | ✓ | | | | | | | |
| | 96 | ✓ | - | | | | | | | |
| | 97 | ✓ | ✓ | | | | | | | |
| | 98 | ✓ | ✓ | | | | | | | |
| | 99 | ✓ | ✓ | | | | | | | |
| | 100 | | ✓ | | | | | | | |
| | 101 | | ✓ | | | | | | | |
| | 102 | | ✓ | | | | | | | |
| | 103 | | ✓ | | | | | | | |
| | 104 | | ✓ | | | | | | | |
| | 105 | | ✓ | | | | | | | |
| | 106 | | ✓ | | | | | | | |

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 3755322 | | 1973-08-28 | Winter et al. | |
| | 2 | 3867383 | | 1975-02-18 | Winter | |
| | 3 | 8133900 | | 2012-03-13 | Hood et al. | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 20090163508 | A1 | 2009-06-25 | KORI et al. | |
| | 2 | 20100129350 | A1 | 2010-05-27 | Zacharie et al. | |
| | 3 | 20120202818 | A1 | 2012-08-09 | Tao et al. | |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

| | | |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 4 | 20120277233 | A1 | 2012-11-01 | Tao et al. | |
| | 5 | 20130190287 | A1 | 2013-07-25 | Cianchetta et al. | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2004050033 | WO | A2 | 2004-06-17 | Arqule, Inc, | | ☐ |
| | 2 | 2005060956 | WO | A1 | 2005-07-07 | University Of Maryland, Baltimore, | | ☐ |
| | 3 | 2009016410 | WO | A2 | 2009-02-05 | Astrazeneca Ab | | ☐ |
| | 4 | 2010144404 | WO | A1 | 2010-12-16 | Abraxis Bioscience, Llc | | ☐ |
| | 5 | 2012160034 | WO | A1 | 2012-11-29 | Bayer Intellectual Property Gmbh, | | ☐ |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 1 | CAIRNS et al. "Oncogenic Isocitrate Dehydrogenase Mutations: Mechanisms, Models, and Clinical Opportunities" Cancer Discovery (2013) Vol 3, Iss 7, pp 730-741 | ☐ |
| | 2 | Cecil Text Book of Medicine, edited by BENNET and PLUM, (1997) 20th edition, Volume 1, pp 1004-1010 | ☐ |
| | 3 | DAVIS et al. "Biochemical, Cellular, and Biophysical Characterization of a Potent Inhibitor of Mutant Isocitrate Dehydrogenase IDH1" The Journal of Biological Chemistry (2014) vol 289, No 20, pp 13717-13725 | ☐ |
| | 4 | DERMER "another Anniversary for the War on Cancer" Bio/Technology (1994) Vol 12, p 320 | ☐ |
| | 5 | FRESHNEY et al. "Culture of Animal Cells, A Manual of Basic Techniques" Alan R. Liss, Inc. (1983) pp 1-6 | ☐ |
| | 6 | GOLUB et al. "Molecular Classification of Cancer: Class Discovery and Class Prediction by Gene Expression Monitoring" Science (1999) Vol 286, pp 531-537 | ☐ |
| | 7 | International Search Report and Written Opinion for International Application No. PCT/US2014/049469 dated January 22, 2015 | ☐ |
| | 8 | KRELL et al., "IDH mutations in tumorigenesis and their potential role as novel therapeutic targets" Future Oncology (2013) Vol 9, Iss 12, pp 1923-1935 | ☐ |
| | 9 | KUSAKABE et al. Chemical Abstracts vol. 152, No. 191956, Abstract for WO2010007756 (2010) | ☐ |
| | 10 | LIU et al. "Inhibition of Cancer-Associated Mutant Isocitrate Dehydrogenases: Synthesis, Structure - Activity Relationship, and Selective Antitumor Activity" Journal of Medicinal Chemistry (2014) vol 57, pp 8307-8318 | ☐ |
| | 11 | PARONIKYAN et al. "Synthesis and biological activity of 3-piperazinylpyrano [3,4-C] pyridines" Armyanskii Khimicheskii Zhurnal (1990) Vol. 43, No. 8, pp 518-523 | ☐ |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 12 | The radiation fact sheet published by the National Cancer Institute, http://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/radiation-fact-sheet, reviewed June 30, 2010 | ☐ |
| | 13 | ZHENG et al. "Synthesis and antitumor evaluation of a novel series of triaminotriazine derivatives" Bioorganic & Medicinal Chemistry (2007) Vol 15, pp 1815-1827 | ☐ |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | /Christopher Adam Hixson/ | Date Considered | 09/04/2015 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Catherine M. McCarty/ | Date (YYYY-MM-DD) | 2015-07-31 |
| Name/Print | Catherine M. McCarty | Registration Number | 54301 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.


ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 3755322 | | 1973-08-28 | Winter et al. | |
| | 2 | 3867383 | | 1975-02-18 | Winter | |
| | 3 | 8133900 | | 2012-03-13 | Hood et al. | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 20090163508 | A1 | 2009-06-25 | KORI et al. | |
| | 2 | 20100129350 | A1 | 2010-05-27 | Zacharie et al. | |
| | 3 | 20120202818 | A1 | 2012-08-09 | Tao et al. | |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 4 | 20120277233 | A1 | 2012-11-01 | Tao et al. | |
| | 5 | 20130190287 | A1 | 2013-07-25 | Cianchetta et al. | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2004050033 | WO | A2 | 2004-06-17 | Arqule, Inc, | | ☐ |
| | 2 | 2005060956 | WO | A1 | 2005-07-07 | University Of Maryland, Baltimore, | | ☐ |
| | 3 | 2009016410 | WO | A2 | 2009-02-05 | Astrazeneca Ab | | ☐ |
| | 4 | 2010144404 | WO | A1 | 2010-12-16 | Abraxis Bioscience, Llc | | ☐ |
| | 5 | 2012160034 | WO | A1 | 2012-11-29 | Bayer Intellectual Property Gmbh, | | ☐ |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 1 | CAIRNS et al. "Oncogenic Isocitrate Dehydrogenase Mutations: Mechanisms, Models, and Clinical Opportunities" Cancer Discovery (2013) Vol 3, Iss 7, pp 730-741 | ☐ |
| | 2 | Cecil Text Book of Medicine, edited by BENNET and PLUM, (1997) 20th edition, Volume 1, pp 1004-1010 | ☐ |
| | 3 | DAVIS et al. "Biochemical, Cellular, and Biophysical Characterization of a Potent Inhibitor of Mutant Isocitrate Dehydrogenase IDH1" The Journal of Biological Chemistry (2014) vol 289, No 20, pp 13717-13725 | ☐ |
| | 4 | DERMER "another Anniversary for the War on Cancer" Bio/Technology (1994) Vol 12, p 320 | ☐ |
| | 5 | FRESHNEY et al. "Culture of Animal Cells, A Manual of Basic Techniques" Alan R. Liss, Inc. (1983) pp 1-6 | ☐ |
| | 6 | GOLUB et al. "Molecular Classification of Cancer: Class Discovery and Class Prediction by Gene Expression Monitoring" Science (1999) Vol 286, pp 531-537 | ☐ |
| | 7 | International Search Report and Written Opinion for International Application No. PCT/US2014/049469 dated January 22, 2015 | ☐ |
| | 8 | KRELL et al., "IDH mutations in tumorigenesis and their potential role as novel therapeutic targets" Future Oncology (2013) Vol 9, Iss 12, pp 1923-1935 | ☐ |
| | 9 | KUSAKABE et al. Chemical Abstracts vol. 152, No. 191956, Abstract for WO2010007756 (2010) | ☐ |
| | 10 | LIU et al. "Inhibition of Cancer-Associated Mutant Isocitrate Dehydrogenases: Synthesis, Structure - Activity Relationship, and Selective Antitumor Activity" Journal of Medicinal Chemistry (2014) vol 57, pp 8307-8318 | ☐ |
| | 11 | PARONIKYAN et al. "Synthesis and biological activity of 3-piperazinylpyrano [3,4-C] pyridines" Armyanskii Khimicheskii Zhurnal (1990) Vol. 43, No. 8, pp 518-523 | ☐ |

EFS Web 2.1.17

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 12 | The radiation fact sheet published by the National Cancer Institute, http://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/radiation-fact-sheet, reviewed June 30, 2010 | ☐ |
| | 13 | ZHENG et al. "Synthesis and antitumor evaluation of a novel series of triaminotriazine derivatives" Bioorganic & Medicinal Chemistry (2007) Vol 15, pp 1815-1827 | ☐ |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | /Christopher Adam Hixson/ | Date Considered | 09/04/2015 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Catherine M. McCarty/ | Date (YYYY-MM-DD) | 2015-07-31 |
| Name/Print | Catherine M. McCarty | Registration Number | 54301 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.


ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

**EAST Search History**

**EAST Search History (Prior Art)**

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| L1 | 1 | "14235513" | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/06/02 10:43 |
| S1 | 1 | "8883438".did. | USPAT | OR | OFF | 2016/05/26 07:56 |
| S2 | 40524 | a61b5/055.cpc. or a61k31/41,426.cpc. or a61k45/06.cpc. or a61k2300/00.cpc. or c12n15/1137.cpc. or c12n2310/14.cpc. or c12q1/32,6886.cpc. or c12y101/01042.cpc. or g01n33/574.cpc. or g06f19/328.cpc. | USPAT | OR | OFF | 2016/05/26 08:02 |
| S3 | 244516 | @pd>="20150904" | USPAT | OR | OFF | 2016/05/26 08:02 |
| S4 | 3065 | S2 and S3 | USPAT | OR | OFF | 2016/05/26 08:02 |
| S5 | 1925 | S4 and cancer | USPAT | OR | OFF | 2016/05/26 08:02 |
| S6 | 0 | S5 and hydroxygluar$4 | USPAT | OR | OFF | 2016/05/26 08:03 |
| S7 | 0 | S5 and hydroxy?gluar$4 | USPAT | OR | OFF | 2016/05/26 08:03 |
| S8 | 130 | S5 and HG | USPAT | OR | OFF | 2016/05/26 08:03 |
| S9 | 117353 | a61b5/055.cpc. or a61k31/41,426.cpc. or a61k45/06.cpc. or a61k2300/00.cpc. or c12n15/1137.cpc. or c12n2310/14.cpc. or c12q1/32,6886.cpc. or c12y101/01042.cpc. or g01n33/574.cpc. or g06f19/328.cpc. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:03 |
| S10 | 527642 | @pd>="20150904" | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:03 |
| S11 | 9087 | S9 and S10 | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:04 |
| S12 | 5579 | S11 and cancer | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:04 |
| S13 | 374 | HG and S12 | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:04 |
| S14 | 6 | (("DANG") near3 ("Leonard")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:08 |

| | | | | | | |
|---|---|---|---|---|---|---|
| S15 | 52 | (("GROSS") near3 ("Stefan")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:09 |
| S16 | 778 | (("JANG") near3 ("Hyun")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:09 |
| S17 | 17 | (("JIN") near3 ("Shengfang")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:09 |
| S18 | 31 | (("SU") near3 ("Shin-San")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:09 |
| S19 | 267 | (("THOMPSON") near3 ("Craig")).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2016/05/26 08:09 |

**6/2/2016 10:44:06 AM**
**C:\Users\chixson\Documents\EAST\Workspaces\13939519-2.wsp**

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | Examiner | Art Unit |
| | CHRISTOPHER A HIXSON | 1797 |

| CPC- SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| A61B5/055 | 26 may 2016 | cah |
| A61K31/41,426 | 26 may 2016 | cah |
| A61K45/06 | 26 may 2016 | cah |
| A61K2300/00 | 26 may 2016 | cah |
| C12N15/1137 | 26 may 2016 | cah |
| C12N2310/14 | 26 may 2016 | cah |
| C12Q1/32,6886 | 26 may 2016 | cah |
| C12Y101/01042 | 26 may 2016 | cah |
| G01N33/574 | 26 may 2016 | cah |
| G06F19/328 | 26 may 2016 | cah |

| CPC COMBINATION SETS - SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| US CLASSIFICATION SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

| SEARCH NOTES | | |
|---|---|---|
| Search Notes | Date | Examiner |
| searched in east as attached, inventor name search, google.com, scholar.google.com | 4 sept 2015 | cah |
| searched in east as attached, inventor name search, google.com, scholar.google.com | 26 may 2016 | cah |

| INTERFERENCE SEARCH |
|---|

| | |
|---|---|
| | |

| US Class/ CPC Symbol | US Subclass / CPC Group | Date | Examiner |
|---|---|---|---|
| | | | |

| | |
|---|---|
| | |

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: February 11, 2016
Electronic Signature for Asimina T. Georges Evangelinos: /Asimina T. Georges Evangelinos/

Docket No.: C2081-701320
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Leonard Luan C Dang et al.

Application No.: 13/939,519 | Confirmation No.: 2110

Filed: July 11, 2013 | Art Unit: 1797

For: METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | Examiner: C. Hixson

**AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111**

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

**INTRODUCTORY COMMENTS**

In response to the Office Action dated September 11, 2015, please amend the above-identified U.S. patent application as follows:

**Amendments to the Claims** begin on page 2 of this paper.

**Remarks/Arguments** begin on page 5 of this paper.

An Information Disclosure Statement (IDS) and a Request for a 2-Month Extension of Time, to and including February 11, 2016, are concurrently being filed with this paper.

## AMENDMENTS TO THE CLAIMS

*Please replace all previously filed claims for the application with the following listing of claims:*

Listing of the Claims:

1-92. (Canceled)

93. (Currently Amended) A method of evaluating a subject for the presence or susceptibility to a cancer comprising analyzing the subject or a sample from the subject for ~~one or more of:~~

[[a) ]]the presence, distribution, or level of 2HG, wherein the subject ~~is not having~~ does not have or is not diagnosed as having 2-hydroxyglutaric aciduria[[;]],

~~b) the presence, distribution, or level of a mutant IDH1 enzyme or mutant IDH2 enzyme, either of which has 2HG neoactivity;~~

~~c) the presence, distribution, or level of a RNA encoding a mutant IDH1 enzyme or mutant IDH2 enzyme, either of which has 2HG neoactivity; or~~

~~d) the presence of DNA encoding a mutant IDH1 enzyme or mutant IDH2 enzyme, either of which has 2HG neoactivity;~~

thereby evaluating the subject for such cancer.

94. (Currently Amended) The method of claim 93, wherein the cancer is selected from the group consisting of an astrocytic tumor, an oligodendroglial tumor, an oligoastrocytic tumor, an anaplastic astrocytoma, fibrosarcoma, paraganglioma, prostate cancer, acute lymphoblastic leukemia, [[or]]and acute myelogenous leukemia.

95. (Previously Presented) The method of claim 93, wherein the cancer is a glioblastoma.

96. (Cancelled) ~~The method of claim 93, the method comprising analyzing the presence, distribution, or level of 2HG.~~

97. (Currently Amended) The method of claim [[96]]93, wherein the presence, distribution or level of 2HG is determined non-invasively by imaging or spectroscopic analysis.

98. (Previously Presented) The method of claim 97, wherein the imaging or spectroscopic analysis comprises magnetic resonance imaging or magnetic resonance spectroscopy.

99. (Currently Amended) The method of claim [[96]]93, wherein the presence, distribution or level of 2HG is determined by evaluating a tissue, product or bodily fluid of the subject.

100. (New) The method of claim 93, wherein the cancer is characterized by a somatic allele, which encodes a mutant IDH enzyme having a neoactivity.

101. (New) The method of claim 100, wherein the mutant IDH enzyme is IDH1.

102. (New) The method of claim 101, wherein the mutant IDH1 enzyme is selected from the group consisting of R132H, R132C, R132S, R132G, R132L, and R132V.

103. (New) The method of claim 100, wherein the mutant IDH enzyme is IDH2.

102. (New) The method of claim 100, wherein the mutation is an IDH2 mutation.

103. (New) The method of claim 102, wherein the IDH2 mutation is selected from the group consisting of R172K, R172M, R172S, R172G, and R172W.

104. (New) The method of claim 93, wherein detecting the presence of 2HG in a subject by magnetic resonance spectroscopy indicates the presence of a cancer in the subject.

105. (New) The method of claim 104, wherein the cancer is a glioma.

106. (New) The method of claim 104, wherein the presence or level of 2HG by magnetic resonance spectroscopy is indicated by a signal at about 2.5ppm.

## REMARKS

Claims Status

Claims 41-99 are pending. Claims 41-92 and 96 are cancelled. Claim 93 is amended. Claim 93 is amended to recite a method of evaluating a subject for the presence or susceptibility to a cancer comprising analyzing the subject or a sample from the subject for the presence, distribution, or level of 2HG, wherein the subject does not have or is not diagnosed as having 2-hydroxyglutaric aciduria, thereby evaluating the subject for such cancer. Support for this amendment can be found, *e.g.*, at least at page 27 of the application as filed. New claims 100 to 107 are added. Claims 100 to 103 find support, *e.g.*, at least at pages 13 and 36-37 of the application as filed. Claims 104 to 106 find support, *e.g.*, at least at pages 26-27 of the application as filed. Upon entry of this amendment, claims 93-95 and 97-106 will be pending. No new matter has been added by these amendments.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 41-56, 63-65 and 80-99 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. In particular, the Office contends that the entire genus of IDH1 and IDH2 mutations encompassed by the claims is not supported by the specification. As a preliminary matter, without acquiescing to the Office's contentions, and solely to expedite prosecution of this application, Applicant has cancelled claims 41-56, 63-65, 80-92 and 96 without prejudice. Independent claim 93 is amended and recites a method of evaluating a subject for the presence or susceptibility to a cancer comprising analyzing the subject or a sample from the subject for the presence, distribution, or level of 2HG, wherein the subject does not have or is not diagnosed as having 2-hydroxyglutaric aciduria, thereby evaluating the subject for such cancer. Applicant submits that claim 93 does not encompass "the entire genus of IDH1 and IDH2 mutations." Claim 93 recites a method of evaluating based on the analysis of 2HG. The IDH1 and IDH2 mutant enzymes having 2HG neoactivity are sufficiently described in the specification. See, *e.g.*, pages 2, 20, and 26-27 of the application as filed. Accordingly, claim 93 and its dependent claims 94-95 and 97-99 are supported by the specification, and Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 41-56, 63-65 and 80-99 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. The Office contends that the phrases "the IDH1 or IDH2 neoactivity phenotype of the subject" and "2HG neoactivity" are functional limitations requiring a sufficient number of representative species to support the claim. Without acquiescing to the Office's contentions, and solely to expedite prosecution of this application, Applicants have cancelled claims 41-45, 63-65, 80-82 and 96 without prejudice. Applicants have amended claim 93 to recite a method of evaluating a subject for the presence or susceptibility to a cancer comprising analyzing the subject or a sample from the subject for the presence, distribution, or level of 2HG, wherein the subject does not have or is not diagnosed as having 2-hydroxyglutaric aciduria, thereby evaluating the subject for such cancer. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph is rendered moot and should be withdrawn.

Rejection under 35 U.S.C. § 101

Claims 41-56, 63-65 and 80-99 are rejected under 35 U.S.C. § 101 as allegedly being directed to subject matter that is not patent eligible. The Office contends that the claims recite an abstract idea, *i.e.*, a judicial exception, and therefore the claims are not patent eligible. Applicants submit that the claims recite something significantly different than an abstract idea, and are thus directed toward patent eligible subject matter. As claims 41-56, 63-65, 80-92 and 96 are cancelled without prejudice, the rejection is applied to claims 93-95 and 97-99, and is respectfully traversed for the following reasons.

The pending claims recite a method of evaluating a subject for the presence or susceptibility to a cancer comprising analyzing the subject or a sample from the subject for the presence, distribution, or level of 2HG, wherein the subject does not have or is not diagnosed as having 2-hydroxyglutaric aciduria, thereby evaluating the subject for such cancer. Thus, the claims recite something significantly different than the judicial exceptions, and are therefore directed toward patent eligible subject matter.

According to the flow chart in the *2014 Interim Guidance on Patent Subject Matter Eligibility* dated December 16, 2014 and the July 30, 2015 update (hereafter "Guidance"), one of the

questions to determine patent eligible subject matter is whether "the claim as a whole recites something significantly different than the judicial exception(s)." In analyzing whether a method claim recites "something significantly different", MPEP § 2106(II)(B) states that a claim "must be limited to a particular practical application." Applicants respectfully submit that the claims recite patent eligible subject matter because they recite methods that are limited to a particular practical application. Claim 93 recites a method that requires analyzing the subject or a sample from the subject for the presence, distribution, or level of 2HG. This analysis requires a practical application, such as spectroscopic analysis, *e.g.*, such as magnetic resonance imaging or magnetic resonance spectroscopy. Applicants submit that the claims require something significantly different, *i.e.*, a particular practical application. Therefore, claim 93 and its dependent claims 94-99 recite patent eligible subject matter, and Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 101.

Rejection under 35 U.S.C. § 102(a)

Claims 93-99 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Aghili *et al.* J. Neurooncology 91, 233-6 (2009) ("Aghili"). Applicants traverse this rejection to the extent that it is maintained over the claims as amended.

MPEP § 2131 provides that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Aghili discloses that patients with 2-hydroxyglutarate dehydrogenase deficiencies accumulate 2HG in the brain as assessed by MRI and CSF analysis. (See, *e.g.*, pages 117 and 118 of the application as filed). Aghili does not disclose a method of evaluating a subject for the presence or susceptibility to a cancer comprising analyzing the subject or a sample from the subject for the presence, distribution, or level of 2HG, wherein the subject does not have or is not diagnosed as having 2-hydroxyglutaric aciduria, thereby evaluating the subject for such cancer. As such, Aghili does not anticipate claim 93 and dependent claims 94-99. Accordingly, the rejection of claims 93-99 under 35 U.S.C. § 102(a) should be withdrawn.

Double Patenting – Nonstatutory

Claims 41-99 are rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over 1-12 of U.S. Patent No. 8,883,438. Applicant respectfully requests that the nonstatutory double patenting rejection be held in abeyance until there is an indication that there is allowable subject matter in this application.

Claims 41-99 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claim 7 of co-pending Application No. 14/504,983. Applicant respectfully requests that the nonstatutory double patenting rejection be held in abeyance until there is an indication that there is allowable subject matter in this application.

## CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Dated: February 11, 2016

Respectfully submitted,

By: /Asimina T. Georges Evangelinos/
Asimina T. Georges Evangelinos
Registration No.: 66,888
LANDO & ANASTASI LLP
Riverfront Office Park
One Main Street
Suite 1100
Cambridge, Massachusetts 02142
(617) 395-7000
Attorney/Agent for Applicant

PTO/AIA/22 (03-13)
Approved for use through 7/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)** | Docket Number (Optional) C2081-701320 |
|---|---|
| Application Number 13/939,519 | Filed July 11, 2013 |
| For METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | |
| Art Unit 1797 | Examiner C. Hixson |

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | | Fee | Small Entity Fee | Micro Entity Fee | |
|---|---|---|---|---|---|
| ☐ | One month (37 CFR 1.17(a)(1)) | $200 | $100 | $50 | $ |
| ☒ | Two months (37 CFR 1.17(a)(2)) | $600 | $300 | $150 | $ 600.00 |
| ☐ | Three months (37 CFR 1.17(a)(3)) | $1,400 | $700 | $350 | $ |
| ☐ | Four months (37 CFR 1.17(a)(4)) | $2,200 | $1,100 | $550 | $ |
| ☐ | Five months (37 CFR 1.17(a)(5)) | $3,000 | $1,500 | $750 | $ |

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50/2762 .

☒ Payment made via EFS-Web.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 66,888 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____ .

/Asimina T. Georges Evangelinos/ — Signature
February 11, 2016 — Date

Asimina T. Georges Evangelinos — Typed or printed name
(617) 395-7015 — Telephone Number

**NOTE:** This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: February 11, 2016 Electronic Signature for Asimina T. Georges Evangelinos: /Asimina T. Georges Evangelinos/

2808317

# PATENT COOPERATION TREATY

# ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

# PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

NTD PATENT AND TRADEMARK AGENCY LIMITED
10th Floor, Block A, Investment Plaza
27 Jinrongdajie, Xicheng District
Beijing 100033
CHINE

Date of mailing *(day/month/year)*
03 January 2014 (03.01.2014)

Applicant's or agent's file reference
P2012873C

IMPORTANT NOTICE

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/CN2012/000841 | 18 June 2012 (18.06.2012) | 17 June 2011 (17.06.2011) |

Applicant
AGIOS PHARMACEUTICALS, INC. et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Lingfei Bai

e-mail: pt02.pct@wipo.int

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>P2012873C | **FOR FURTHER ACTION** | See item 4 below |
| International application No.<br>PCT/CN2012/000841 | International filing date *(day/month/year)*<br>18 June 2012 (18.06.2012) | Priority date *(day/month/year)*<br>17 June 2011 (17.06.2011) |
| International Patent Classification (8th edition unless older edition indicated)<br>See relevant information in Form PCT/ISA/237 | | |
| Applicant<br>AGIOS PHARMACEUTICALS, INC. | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☒ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

| | |
|---|---|
| | Date of issuance of this report<br>17 December 2013 (17.12.2013) |
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br>Facsimile No. +41 22 338 82 70 | Authorized officer<br>Lingfei Bai<br>e-mail: pt02.pct@wipo.int |

Form PCT/IB/373 (January 2004)

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

100033

10th Floor, Block A Investment Plaza 27
Jinrongdajie,Xicheng District, Beijing 100033
China

NTD PATENT & TRADEMARK AGENCY LTD

# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43 *bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 27 Sep. 2012 (27.09.2012) |
| Applicant's or agent's file reference | **FOR FURTHER ACTION** |
| P2012873C | See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/CN2012/000841 | 18 Jun. 2012(18.06.2012) | 17 Jun. 2011(17.06.2011) |

International Patent Classification (IPC) or both national classification and IPC

See Supplemental Box

Applicant

AGIOS PHARMACEUTICALS,INC. et al.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No.II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No.VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No.VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of **3** months from the date of mailing of Form PCT/ISA/220 or before the expiration of **22** months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/CN | Date of completion of this opinion | Authorized officer |
|---|---|---|
| The State Intellectual Property Office, the P.R.China<br>6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088<br>Facsimile No. 86-10-62019451 | 10 Sep. 2012 (10.09.2012) | HAO,Peng<br>Telephone No.<br>(86-10)82246764 |

Form PCT/ISA/237(cover sheet)( July 2009)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/000841

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.
   ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application ,this opinion has been established on the basis of :

   a. a sequence listing filed or furnished

      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing

      ☐ contained in the applicant as filed
      ☐ filed together with the application in electronic form
      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/000841

**Box No.III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

This questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious),or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-3(part), 4, 5-21(part), 22-25

because:

☒ the said international application, or the said claims Nos. 22-25
relate to the following subject matter which does not require an international search (*specify*):
See Box No. II in PCT/ISA/210.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 1-3(part), 4, 5-25(part) are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):
See Box No. II in PCT/ISA/210.

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule **13ter.1(a) or (b).**

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/000841

**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement:

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-3(part), 5-25(part) | YES |
| | Claims | NONE | NO |
| Inventive step (IS) | Claims | NONE | YES |
| | Claims | 1-3(part), 5-25(part) | NO |
| Industrial applicability (IA) | Claims | 1-3(part), 5-25(part) | YES |
| | Claims | NONE | NO |

2. Citations and explanations

The explanations of claim 6 with regard to novelty, inventive step or industrial applicability are made based on that claim 6 is a dependent claim of claim 5. (see Box No. VIII)

The explanations of claim 12 with regard to novelty, inventive step or industrial applicability are made based on its general scope. (see Box No. VIII).

Reference is made to the following document:

D1: WO 2010/007756 A1 (SHIONOGI & CO., LTD. et al.) 21 Jan. 2010 (21. 01. 2010)

**I. Novelty**

D1 discloses compounds with formula I especially with the structure of example 2-272 and example 2-343 which are used to treat cancer (see claims 1, 19-25, example 2-272, example 2-343 of description).

No relevant compounds falling into the scope of present claim 1 as defined that Y is $-N(R^5)-$ and $R^4$ is selected from –CN or $C(O)-O-C_1-C_4$ alkyl are disclosed by D1. Therefore, the present claim 1 is novel in the sense of Article 33(2) PCT. For the same reason, dependent claims 2-3, 5-19 and claims 20-25 comprising the compounds of claim 1 are also novel in the sense of Article 33(2) PCT.

**II. Inventive step**

For claim 1, D1 is considered as the closest prior art. The compound in D1 which is structurally closest to the presently claimed compounds is example 2-272 in table 6 of description. Said compound corresponds to a compound of present formula (I) in claim 1 wherein $R^2$=4-MeCONH-Ph, $R^{1b}$=H, $R^{1a}$=5-methylfuran-2-yl, $R^4$=CN, m=0, $R^5$=furan-2-yl-CO-. The difference between claim 1 and D1 is that $R^2$ in present claim 1 is phenyl which can be substituted by methyl or fluoro. Though the compounds in present claim 1 are said to be the inhibitors of IDH1 mutants, while the compounds in D1 are described as inhibitors of TTK protein kinase, both of them are used to treat cancer. Thus, the technical problem to be solved by the present claim can be seen in provision of alternative compounds for the treatment of cancer. D1 also discloses that $R^5$ (equal to $R^2$ in the present claim 1) in formula I could be substituted aryl group and the substitute could be methyl or halide (see paragraph [0123] of description and claim 1 in D1). Therefore, it appears obvious for a person skilled in the art to modify the compound of example 2-272 in D1 by changing 4-MeCONH-Ph into phenyl substituted by methyl or fluoro in order to acquire the subject matter of claim 1. Accordingly, claim 1 does not involve an inventive step in the sense of Article 33(3) PCT.

Claims 2-3, 5-19 further define claim 1. The additional technical feature of different groups is a customary option in the art. Therefore, claims 2-3, 5-19 do not involve an inventive step in the sense of Article 33(3) PCT.

Since D1 discloses example 2-272 as inhibitor of TTK protein kinase, pharmaceutical composition comprising this compound and its use in manufacture of a medicament for treating cancer, the present claims 20-21 for pharmaceutical compositions and claims 22-25 for use are not considered inventive and do not involve an inventive step in the sense of Article 33(3) PCT.

**III. Industrial applicability**

The subject matter of claims 1-3, 5-25 can be made or used in pharmaceutical industry, so the subject matter of claims 1-3, 5-25 meets the criteria of Article 33(4) PCT.

**Box No. VII Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

1. Multiple dependent claims 18-19 refer to other multiple dependent claims, so claims 18-19 do not meet the requirements of Rule 6.4(a) PCT.

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. The present claim 1 relates to an extremely large number of possible compounds. Support and disclosure in the sense of Article 6 and 5 PCT are to be found however for only a very small proportion of the compound claimed, (see exemplary compounds 100-829 on pages 24-95). Thus, claim 1 does not meet the criteria set out in Article 6 and 5 PCT. As the same reason, claims 2-25 do not meet the criteria set out in Article 6 and 5 PCT too.
2. Claim 6 is a dependent claim of claim 6, which renders the protection scope unclear. Thus, claim 6 does not meet the criteria set out in Article 6 PCT. The written opinion has been made based that claim 6 is a dependent claim of claim 5.
3. There is a bracket in claim 12, so claim 12 simultaneously involves a general scope and a preferred scope, which renders the protection scope of the said claim unclear. Thus, claim 12 does not meet the criteria set out in Article 6 PCT. The written opinion has been made based on the general scope.

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of : International Patent Classification (IPC) or both national classification and IPC

C07D 401/04 (2006.01) i

C07D 401/02 (2006.01) i

C07D 401/14 (2006.01) i

C07D 405/00 (2006.01) i

A61K 31/44 (2006.01) i

A61K 31/4427 (2006.01) i

A61P 35/00 (2006.01) i

# PATENT COOPERATION TREATY

# ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

# PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

NTD PATENT AND TRADEMARK AGENCY LIMITED
10th Floor, Block A, Investment Plaza
27 Jinrongdajie, Xicheng District
Beijing 100033
CHINE

Date of mailing *(day/month/year)*
03 January 2014 (03.01.2014)

Applicant's or agent's file reference
P2012874C

IMPORTANT NOTICE

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/CN2012/077096 | 18 June 2012 (18.06.2012) | 17 June 2011 (17.06.2011) |

Applicant
AGIOS PHARMACEUTICALS, INC. et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Lingfei Bai

e-mail: pt02.pct@wipo.int

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>P2012874C | **FOR FURTHER ACTION** | See item 4 below |
| International application No.<br>PCT/CN2012/077096 | International filing date *(day/month/year)*<br>18 June 2012 (18.06.2012) | Priority date *(day/month/year)*<br>17 June 2011 (17.06.2011) |
| International Patent Classification (8th edition unless older edition indicated)<br>See relevant information in Form PCT/ISA/237 | | |
| Applicant<br>AGIOS PHARMACEUTICALS, INC. | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

| | |
|---|---|
| | Date of issuance of this report<br>17 December 2013 (17.12.2013) |
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br>Facsimile No. +41 22 338 82 70 | Authorized officer<br>Lingfei Bai<br>e-mail: pt02.pct@wipo.int |

Form PCT/IB/373 (January 2004)

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

100033

10th Floor, Block A Investment Plaza 27
Jinrongdajie,Xicheng District, Beijing 100033
China

NTD PATENT & TRADEMARK AGENCY LTD

# PCT

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

(PCT Rule 43 *bis*.1)

| | |
|---|---|
| | Date of mailing *(day/month/year)* 04 Oct. 2012 (04.10.2012) |
| Applicant's or agent's file reference P2012874C | **FOR FURTHER ACTION** See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/CN2012/077096 | 18 Jun. 2012(18.06.2012) | 17 Jun. 2011(17.06.2011) |

International Patent Classification (IPC) or both national classification and IPC
See Supplemental Box

Applicant
AGIOS PHARMACEUTICALS, INC. et al.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No.II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No.VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No.VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of **3** months from the date of mailing of Form PCT/ISA/220 or before the expiration of **22** months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/CN | Date of completion of this opinion | Authorized officer |
|---|---|---|
| The State Intellectual Property Office, the P.R.China<br>6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088<br>Facsimile No. 86-10-62019451 | 17 Sep. 2012 (17.09.2012) | ZHAO, Zhenzhen<br>Telephone No.<br>(86-10) 62086358 |

Form PCT/ISA/237(cover sheet)( July 2009)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/077096

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.
   ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application ,this opinion has been established on the basis of :

   a. a sequence listing filed or furnished

      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing

      ☐ contained in the applicant as filed
      ☐ filed together with the application in electronic form
      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/077096

**Box No.III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

This questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious),or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 32-35

because:

☒ the said international application, or the said claims Nos. 32-35
relate to the following subject matter which does not require an international search (*specify*):

See PCT/ISA/210 Box No. II 1.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule **13ter.1(a) or (b).**

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/077096

**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement:

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 6-8, 11-13, 15-29, 31-35 | YES |
| | Claims | 1-5, 9-10, 14, 30 | NO |
| Inventive step (IS) | Claims | 6-8, 11-13, 15-29, 31-35 | YES |
| | Claims | 1-5, 9-10, 14, 30 | NO |
| Industrial applicability (IA) | Claims | 1-35 | YES |
| | Claims | NONE | NO |

2. Citations and explanations

This written opinion is established on the basis of subject matter anticipated reasonably, please see Box No. III and Box No. VIII for more details.

2.1 Reference is made to the following documents:

D1: SIRAKANYAN, S. N. et al. Synthesis of new derivatives of piperazine-substituted pyrano[3, 4- c]pyridines. Hayastani Kimiakan Handes 2009, Vol. 62, No. 3-4, pages 378-385, ISSN:1561-4190

D2: JP 9291034 A(Yoshitomi Pharmaceutical Industries, Ltd.) 11 Nov.1997 (11.11.1997)

D3: JP 4099768 A (Dainippon Seiyaku K. K.) 31 Mar.1992 (31. 03. 1992)

D4: EP 385237 A2 (Dainippon Pharmaceutical Co., Ltd.) 05 Sep. 1990 (05. 09. 1990)

D5: EP 384228 A1 (Dainippon Pharmaceutical Co., Ltd.) 29 Aug. 1990 (29. 08. 1990)

D6: CHEM ABSTRACT No. 115: 29158 & Paronikyan, E. G. et al. Synthesis and biological activity of 3-piperazinylpyrano[3,4-c]pyridines. Armyanskii Khimicheskii Zhurnal 1990, Vol. 43, No. 8, pages 518-23

2.2 Novelty

The present application claims compounds of formula (I), pharmaceutical compositions , and the use of the compositions in the manufacture of corresponding medicaments.

The compounds 4a, 4b, 4g, 4h, 4i disclosed in D1 (see page 379 of D1) have fallen into the scopes of claims 1-5, 9.

The compounds 37, 40, 43, 47, 49, 53-57, 59-63, 66-74 disclosed in D2 (see pages 16-23 of D2) have fallen into the scopes of claims 1, 4, 9-10.

See Supplemental Box

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Dependent claim 19 refers to claim 18, however, the definition of "$R^2$ is selected from ethyl" in claim 19 goes beyond the scope of "$R^2$" in claim 18. Therefore, claim 19 is unclear and does not comply with PCT Article 6.

Dependent claim 22 refers to claim 120, however, claim 120 does not exist. Therefore, claim 22 is unclear and does not comply with PCT Article 6.

Claim 28 does not define substituents of $R^{3a}$, $R^{3b}$, $R^{3c}$, $R^{3d}$ present in the formula of said claim. Thus claim 28 is unclear and does not comply with PCT Article 6.

This written opinion is established on the basis of subject matter anticipated reasonably, i.e., definition of $R^2$ in claim 19 can also be ethyl, and claim 22 refers to claim 20, and definitions of $R^{3a}$, $R^{3b}$, $R^{3c}$, $R^{3d}$ in claim 28 are the same as that in page 16 of the description.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of :

cover sheet :International Patent Classification (IPC) or both national classification and IPC

C07D 491/052 (2006.01) i

C07D 217/26 (2006.01) i

C07D 413/04 (2006.01) i

C07D 519/00 (2006.01) i

A61K 31/496 (2006.01) i

A61P 35/00 (2006.01) i

Continuation of :

Box No. V:Citations and explanations

The compound 22 disclosed in D3 (see page 454, Table 4 of D3) has fallen into the scopes of claims 1, 4, 9-10.

The compounds 14-20, 57-60, 66-67, 115, 128 disclosed in D4 (see pages 29-31, 37-38, Table 12-13 of D4) have fallen into the scopes of claims 1, 4, 9-10, and the compound 128 disclosed in D4 (see page 38 of D4) has also fallen into the scope of claim 14.

The compounds 25-30, 33, 41-43 disclosed in D5 (see page 20-21, Table 10-11 of D5) have fallen into the scopes of claims 1, 4, 9-10.

The compounds CAS no. 134538-28-6, 134538-29-7, 134538-30-0, 134538-31-1 disclosed in D6 have fallen within the scopes of claims 1-5, 9-10, 14.

Thus, claims 1-5, 9-10, 14 are not novel, and do not meet the criteria set out in PCT Article 33(2).

The compounds 37, 40, 43, 47, 49, 53-57, 59-63, 66-74 disclosed in D2 (see pages 16-23 of D2) , and the compounds 14-20, 57-60, 66-67, 115, 128 disclosed in D4 (see pages 29-31, 37-38, Table 12-13 of D4) have fallen into the scope of claim 1. D2 and D4 also disclose compositions of said compounds (see claim 4 of D2, claim 16 of D4). So the composition claimed in claim 30 is disclosed by D2 and D4. Thus, claim 30 is not novel, and does not meet the criteria set out in PCT Article 33(2).

See Supplemental Box

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of :

Box No. V:Citations and explanations

The subject matter of claims 6-8, 11-13, 15-29, 31-35 differs from D1-D6 in structure of the compounds and/or the pharmaceutical uses of the compounds. Thus the subject matter of claims 6-8, 11-13, 15-29, 31-35 is therefore new (Article 33(2) PCT).

2.3 Inventive step

The compounds or pharmaceutical compositions disclosed in D1-D6 of claims 1-5, 9-10, 14, 30 are not novel, so the compounds or pharmaceutical compositions disclosed in D1-D6 of claim 1-5, 9-10, 14, 30 could not be considered as involving an inventive step, and does not meet the criteria set out in Article 33(3) PCT.

The compounds or pharmaceutical compositions which are not disclosed in D1-D6 of claims 1-5, 9-10, 14, 30, and claims 6-8, 11-13, 15-29, 31-35 differ from D1-D6 in structure of the compounds and/or the pharmaceutical uses of the compounds.

There is no teaching in the prior arts that would prompt the skilled person in the art to use the compounds of D1-D6 as the inhibition of mutant IDH1. Therefore, it is not obvious for a person skilled in the art to obtain the compounds or pharmaceutical compositions which are not disclosed in D1-D6 of claims 1-5, 9-10, 14, 30, and claims 6-8, 11-13, 15-29, 31-35 based on D1-D6. Accordingly, the compounds or pharmaceutical compositions which are not disclosed in D1-D6 of claims 1-5, 9-10, 14, 30, and claims 6-8, 11-13, 15-29, 31-35 involve an inventive step and meet the criteria set out in Article 33(3) PCT.

2.4 Industrial applicability

The subject matter of claims 1-35 can be made or used in pharmaceutical industry and thus meets the requirements of Article 33(4) PCT.

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
CATHERINE M. MCCARTY
LANDO & ANASTASI LLP
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

**PCT**

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

| | |
|---|---|
| Applicant's or agent's file reference<br>C2081-7054WO | Date of mailing *(day/month/year)*<br>**FOR FURTHER ACTION** See paragraphs 1 and 4 below |
| International application No.<br>PCT/US 13/64601 | International filing date *(day/month/year)*<br>11 October 2013 (11.10.2013) |
| Applicant AGIOS PHARMACEUTICALS, INC. | |

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   **Filing of amendments and statement under Article 19:**
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   **When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   **Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   **For more detailed instructions**, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

| | |
|---|---|
| Name and mailing address of the ISA/<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>Telephone No. PCT OSP: 571-272-7774 |

Form PCT/ISA/220 (July 2010)

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
CATHERINE M. MCCARTY
LANDO & ANASTASI LLP
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

| | |
|---|---|
| | Date of mailing *(day/month/year)* 24 FEB 2014 |
| Applicant's or agent's file reference C2081-7054WO | **FOR FURTHER ACTION** See paragraphs 1 and 4 below |
| International application No. PCT/US 13/64601 | International filing date *(day/month/year)* 11 October 2013 (11.10.2013) |
| Applicant AGIOS PHARMACEUTICALS, INC. | |

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   **Filing of amendments and statement under Article 19:**
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   **When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   **Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   **For more detailed instructions**, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

| | |
|---|---|
| Name and mailing address of the ISA/<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>Telephone No. PCT OSP: 571-272-7774 |

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference C2081-7054WO | **FOR FURTHER ACTION** | see Form PCT/ISA/220 as well as, where applicable, item 5 below. |
|---|---|---|
| International application No. PCT/US 13/64601 | International filing date *(day/month/year)* 11 October 2013 (11.10.2013) | (Earliest) Priority Date *(day/month/year)* 15 October 2012 (15.10.2012) |
| Applicant AGIOS PHARMACEUTICALS, INC. | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

**Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)**

Provided are compounds aryl sulfonamide diarylurea derivatives that are inhibitors of mutant isocitrate dehydrogenase (IDH 1/2), useful for treating cancer and methods of treating cancer comprising administering to a subject in need thereof a compound described here. cancers treatable by the compounds of the invention are glioblastoma, myeloplastic syndrome, myeloproliferative neoplasm, acute myelogenous leukemia, sarcoma, melanoma, non-small cell lung cancer, chondrosarcoma and non-Hodgekin's lymphoma (NHL).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/64601

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/17; A61K 31/18 (2014.01)
USPC - 514/595; 514/601-602
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 31/17; A61K 31/18 (2014.01)
USPC - 514/595; 514/601-602

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/588, 593, 596, 604

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase, PubWest (pgpb, uspt, usoc, epab, jpab, dwpi, tdbd), Dialog Proquest (npl), Google Patents (pl, npl), Google scholar (pl, npl); Search Terms: benzenesulfonamide, sulfonyl, phenylsulfonylamino, urea, phenylurea, diphenylurea, isocitrate dehydrogenase, IDH1, IDH2 mutation, cancer, inhibitor, IDH, naph-dependent, sulfonamide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>---<br>Y<br>---<br>A | PUBCHEM CID 4078245 [online]; 13 September 2005 (13.09.2005) [retrieved on 04.02.2012]; retrieved from http://pubchem.ncbi.nlm.nih.gov/; 2D-structure | 1-2, 4-5<br>---<br>7-8<br>---<br>6, 9-16 |
| X<br>---<br>A | PUBCHEM CID 4854170 [online]; 17 September 2005 (17.09.2005) [retrieved on 04.02.2012]; retrieved from http://pubchem.ncbi.nlm.nih.gov/; 2D-structure | 1, 3<br>---<br>6, 9-16 |
| Y | US 2003/0109527 A1 (JIN, et al.) 12 June 2003 (12.06.2003) entire document, especially para [0010], [0862] | 7-8 |
| Y | US 2012/0164143 A1 (TEELING, et al.) 28 June 2012 (28.06.2012) entire document, especially para [0022], [0027] | 8 |
| A | US 2009/0093526 A1 (MILLER, et al.) 09 April 2009 (09.04.2009) entire document, especially para [0089] | 6, 9-16 |
| A | WO 2011/050210 A1 (SU, et al.) 28 April 2011 (28.04.2011) entire document, especially pg 3, 216 | 6, 9-16 |

☒ 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 |
|---|---|
| 04 February 2014 (04.02.2014) | 24 FEB 2014 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | POPOVICI-MULLER, et al. "Discovery of the first potent inhibitors of mutant IDH1 that lower tumor 2-HG in vivo." ACS Medicinal Chemistry Letters, 2012 [Published: September 17, 2012], Vol.3, pp 850-855. Entire Document. | 6, 9-16 |
| A | WO 2012/009678 A1 (POPOVICI-MULLER, et al.) 19 January 2012 (19.01.2012) entire document, especially pg 2 | 6, 9-16 |

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: CATHERINE M. MCCARTY
LANDO & ANASTASI LLP
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

# PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 24 FEB 2014 |
| Applicant's or agent's file reference<br>C2081-7054WO | **FOR FURTHER ACTION**<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US 13/64601 | 11 October 2013 (11.10.2013) | 15 October 2012 (15.10.2012) |

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/17; A61K 31/18 (2014.01)
USPC - 514/595; 514/601-602

Applicant AGIOS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Fom PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

| Name and mailing address of the ISA/US | Date of completion of this opinion | Authorized officer: |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | 04 February 2014 (04.02.2014) | Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 13/64601

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 13/64601

**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 6-16 | YES |
| | Claims | 1-5 | NO |
| Inventive step (IS) | Claims | 6, 9-16 | YES |
| | Claims | 1-5, 7-8 | NO |
| Industrial applicability (IA) | Claims | 1-16 | YES |
| | Claims | None | NO |

2. Citations and explanations:

Claims 1-2 and 4-5 lack novelty under PCT Article 33(2) as being anticipated by PubChem CID 4078245 (hereinafter 'CID 4078245').

As to claim 1, CID 4078245 discloses a compound of Formula (I) [pictured structure] wherein
each R1 is H;
L1 is a bond;
A1 is an aryl;
A2 is an aryl;
L2 is a -NR5-;
R2 is C1 haloalkyl;
R3 is a aryl substituted with one R6 wherein R6 is a halo;
R4 is C1alkyl;
R5 is H;
and n is 1 provided that:
when L2 is -N(R5)- wherein R5 is H, A2 is phenyl, and R4 is methyl and R4 is para to the N(R1)C(O)N(R1) moiety, then R3 is not methyl;
and is not the one of the listed compounds (pg 1, Fig).

As to claim 2, CID 4078245 discloses the compound of claim 1, wherein the compound is a compound of Formula (II): [pictured structure] wherein X is CH and L1, L2, A1, R2, R3, R4, R5, R6, R7 and n are as defined in Formula (I); provided that: when L2 is -N(R5)- wherein R5 is H, A2 is phenyl, and R4 is methyl and R4 is para to the N(R1)C(O)N(R1) moiety, then R3 is not methyl;
and is not the one of the listed compounds (pg 1, Fig).

As to claim 4, CID 4078245 discloses the compound of claim 1, wherein the compound is a compound of Formula (IV) wherein L1, L2, A1, R2, R3, R4, R5, R6, R7 and n are as defined in Formula (I) provided that: when L2 is -N(R5)- wherein R5 is H, and R4 is methyl then R3 is not methyl; and is not the one of the listed compounds (pg 1, Fig)

As to claim 5, CID 4078245 discloses the compound of claim 1, wherein the compound is compound 221 from Table 1 (pg 1, Fig).

Claims 1 and 3 lack novelty under PCT Article 33(2) as being anticipated by PubChem CID 4854170 (hereinafter 'CID 4854170').

As to claim 1, CID 4854170 discloses a compound of Formula (I) [pictured structure] wherein
each R1 is H;
L1 is a bond;
A1 is an aryl;
A2 is an aryl;
L2 is a -NR5-;
R2 is a halo;
R3 is an aryl substituted with one R6 wherein R6 is a halo;
R4 is halo;
R5 is H;
and n is 1 provided that the compound is not the one of the listed compounds (pg 1, Fig).

As to claim 3, CID 4854170 discloses the compound of claim 1, wherein the compound is a compound of Formula (III) wherein X, A1, R2, R3, R4, R5, R6, R7 and n are as defined in Formula (I) provided that provided that the compound is not the one of the listed compounds (pg 1, Fig).

----Please See Continuation in Supplemental Box----

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:
Box V, Citations and Explanation:

Claim 7 lacks an inventive step under PCT Article 33(3) as being obvious over CID 4078245 in view of US 2003/0109527 A1 to Jin, et al. (hereinafter 'Jin').

As to claim 7, CID 4078245 discloses the compound of claim 1, but does not disclose a pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier. However, Jin discloses a pharmaceutical composition useful in treating IL-8 mediated diseases (para [0001]) comprising a sulfonamide diphenyl urea compound similar to that of claim 1, and a pharmaceutically acceptable carrier (para [0010]). It would have been obvious to one of ordinary skill in the art to combine the compound disclosed by CID 4078245 with the pharmaceutical composition disclosed by Jin because Jin discloses wherein the composition includes sulfonamide diphenyl urea compounds (para [0001]) and produce a composition as claimed having potential utility in the treatment of IL-8 mediated disorders.

Claim 8 lacks an inventive step under PCT Article 33(3) as being obvious over CID 4078245 in view of Jin and further in view of US 2012/0164143 A1 to Teeling, et al. (hereinafter 'Teeling').

As to claim 8, CID 4078245 in view of Jin discloses the composition of claim 7, but does not disclose the composition comprising a second therapeutic agent useful in the treatment of cancer. However, Teeling discloses the use of an IL-8 antibody with an additional therapeutic agents (para [0022]) wherein those therapeutic agents are used to treat cancer (para [0022], i.e. chemotherapuetic agents). It would have been obvious to one of ordinary skill in the art to combine the composition disclosed by CID 4078245 in view of Jin, having potential utility in the treatment of an IL-8 mediated disorder, with the teachings of Teeling because Teeling discloses wherein the composition comprises an IL-8 antibody used to treat IL-8 mediated diseases including tumors (para [0027]) and Jin discloses wherein the composition is an IL-8 receptor antagonist used to treat IL-8 diseases including tumors (para [0862]). Therefore, the composition of claim 8 would have been obvious to one of ordinary skill in the art through routine experimentation.

Claims 6 and 9-16 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed subject matter, specifically the compound of Formula I of Table 2 or use of a compound of Formula I in a method of treating a cancer characterized by the presence of an IDH2 or an IDH1 mutation.

The best prior art on record that disclose compounds similar to Formula I listed in Table 2 are below:

CID 4078245 discloses a compound of Formula I, but does not disclose wherein the composition includes a compound listed in Table 2.

CID 4854170 discloses a compound of Formula I, but does not disclose wherein the composition includes a compound listed in Table 2.

US 2009/0093526 A1 to Miller, et al. (hereinafter 'Miller') discloses a compound similar to Formula I (para [0089], i.e. N-(5-(Difluoromethanesulfonyl)-2-methoxyphenyl)-N'-(4-fluoro-3-methylphenyl)urea), but does not disclose wherein when L2 is a bond, R3 is heterocyclyl and does not disclose wherein the compound is of Formula I or wherein the compound is an IDH inhibitor.

The best prior art on record that disclose inhibitors of mutant IDH are below:

WO 2011/050210 A1 to Su, et al. (hereinafter 'Su') discloses a compound similar to Formula I (pg 216, Compound 33) wherein the compound is an IDH modulator (pg 3, second paragraph), but does not disclose wherein the compound has the structure of Formula I.

The article entitled "Discovery of the first potent inhibitors of mutant IDH1 that lower tumor 2-HG in vivo', by Popovici-Muller, et al. (hereinafter 'Popovici-Muller') discloses IDH1 inhibitor compounds (pg 850), but the compounds do not have the structure of Formula I (pg 851).

WO 2012/009678 A1 to POPOVICI-MULLER, et al. hereinafter 'Muller '678') discloses a IDH1 inhibitor (pg 2, para 2-3), but does not disclose wherein the compound has the structure of Formula I.

There is no prior art on record that discloses the claimed subject matter, specifically therapeutic utility of a compound of Formula I as an IDH inhibitor or a compound of Table 2. Thus, claims 6 and 9-16 meet the criteria set out in PCT Article 33(2)-(3).

Claims 1-16 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

SEARCH HISTORY

| | |
|---|---|
| **Application Number** | PCT/US 13/64601 |
| **Search Conducted By** | KW |
| **Search Approved By** | MSS |

| | |
|---|---|
| **US/IPC Classifications Searched** | IPC(8) -A61K 31/17; A61K 31/18 (2014.01)<br>USPC - 514/595; 514/601-602 |
| **Date Conducted** | 29 January 2014 (29.01.2014) - 04 February 2014 (04.02.2014) |

| | |
|---|---|
| **Documentation Searched** | USPC: 514/588, 593, 596, 604 |
| **Search Terms Used** | benzenesulfonamide, sulfonyl, phenylsulfonylamino, urea, phenylurea, diphenylurea, isocitrate dehydrogenase, IDH1, IDH2 mutation, cancer, inhibitor, IDH, naph-dependent, sulfonamide, formula, structure, myelodysplastic, glioma, myelogenous, sarcoma, IL-8, receptor, antagonist, second, therapeutic |
| **Date Conducted** | 29 January 2014 (29.01.2014) - 04 February 2014 (04.02.2014) |

| | |
|---|---|
| **Electronic Database Searched** | Google Patents |
| **Files Searched** | PL |
| **Date Conducted** | 29 January 2014 (29.01.2014) - 04 February 2014 (04.02.2014) |

**Search Logic:**

sulfonamide IDH inhibitor = 9,810 results
sulfonamide IDH1 inhibitor = 284 results
phenylsulfonylamino idh = 7 results
phenylsulfonylamino urea cancer = 2,940 results
phenylsulfonylamino urea cancer naph = 1,670 results
phenylsulfonylamino urea cancer NAPH-dependent = 1,130 results
phenylsulfonylamino urea cancer isocitrate dehydrogenase = 4 results
urea cancer isocitrate dehydrogenase = 6,550 results
phenylurea cancer isocitrate dehydrogenase = 2 result

SEARCH HISTORY

| | |
|---|---|
| **Electronic Database Searched** | Google Scholar |
| **Files Searched** | PL, NPL |
| **Date Conducted** | 29 January 2014 (29.01.2014) - 04 February 2014 (04.02.2014) |
| **Search Logic:** | |

idh1 inhibitor cancer sulfonamide = 55 results
idh1 inhibitor cancer = 5,970 results
idh1 idh2 inhibitor cancer = 3,020 results
idh1 idh2 sulfonamide cancer = 35 results
idh1 idh2 sulfonamide = 93 results
idh1 idh2 cancer inhibitor urea = 157 results
idh1 idh2 cancer inhibitor urea naph = 70 results
idh1 idh2 cancer inhibitor urea formula = 26 results
idh1 idh2 cancer inhibitor phenyl sulfonyl amino = 14 results
idh1 idh2 cancer phenylsulfonylamino = 0 results
idh1 idh2 cancer phenylurea = 1 result
idh1 idh2 cancer sulfonyl = 36 results
idh2 mutation cancer urea sulfonyl = 7 results
idh mutation cancer urea sulfonyl = 16 results
benzene sulfonamide urea myelodysplastic = 583 results
phenylsulfonamide urea myelodysplastic = 8 results
"IL-8" receptor antagonist cancer second therapeutic = 25,500 results
"IL-8" "receptor antagonist" cancer second therapeutic = 21,400 results
"IL-8 receptor antagonist" cancer second therapeutic = 4 results

| | |
|---|---|
| **Electronic Database Searched** | Dialog ProQuest |
| **Files Searched** | Databases: ABI/INFORM® Professional Standard, AGRICOLA, AGRIS, Allied & Complementary Medicine™, Analytical Abstracts, British Library Inside Conferences, British Nursing Index, Business & Industry, Business Monitor International, Chemical Business Newsbase, Chemical Engineering & Biotechnology Abstracts, Current Contents® Search, Dialog Global Reporter, Economist Intelligence Unit, Ei EnCompassLIT, Emerging Markets Direct, Energy Science and Technology, ESPICOM Pharmaceutical & Medical Device News, FDAnews, FLUIDEX (Fluid Engineering Abstracts), Gale Group Computer Database™, Gale Group Health Periodicals Database, Gale Group New Product Announcements / Plus®, Gale Group Newsletter Database™, Gale Group PharmaBiomed Business Journals, Gale Group PROMT®, Gale Group Trade & Industry Database™, GEOBASE , HSELINE: Health and Safety, ICONDA - International |

| | |
|---|---|
| | Construction Database, Inspec®, Jane's Defense & Aerospace News, Lancet Titles, Material Safety Datasheets -OHS™, MEDLINE®, New England Journal of Medicine, Paperbase, PAPERCHEM, PASCAL, PIRABASE, ProQuest Biological & Health Science Professional, ProQuest Environmental Science Professional, ProQuest Newsstand Professional, ProQuest Research, ProQuest Technology Research Professional, Registry of Toxic Effects of Chemical Substances (RTECS®), Toxfile®, Transport Research International Documentation, TULSA™ (Petroleum Abstracts), UBM Computer Full Text, Weldasearch®, World News Connection |
| **Date Conducted** | 29 January 2014 (29.01.2014) - 04 February 2014 (04.02.2014) |

Set#: S1 Searched for: idh* inhibitor* *sulfonamide* Results: 7°

Set#: S2 Searched for: idh* inhibitor* cancer* agios* Results: 71°

Set#: S3 Searched for: (idh* inhibitor* cancer* agios*) AND pd(19000101-20121015) Results: 25°

Set#: S4 Searched for: idh* inhibitor* cancer* Results: 378°

Set#: S5 Searched for: (idh* inhibitor* cancer*) AND pd(19000101-20121015) Results: 260°

Set#: S6 Searched for: idh* inhibitor* cancer* (formula or structure) Results: 84°

Set#: S7 Searched for: (idh* inhibitor* cancer* (formula OR structure)) AND pd(19000101-20121015) Results: 56°

Set#: S8 Searched for: idh* *sulfonamide* Results: 14°

Set#: S9 Searched for: (idh* *sulfonamide*) AND pd(19000101-20121015) Results: 9°

Set#: S10 Searched for: an("000309348600007") Results: 1

Set#: S1 Searched for: idh *urea* Results: 211°

Set#: S2 Searched for: (idh1 or ihd2) *urea* Results: 48°

Set#: S3 Searched for: ((idh1 OR ihd2) *urea*) AND pd(19000101-20121015) Results: 33°

SEARCH HISTORY

Set#: S4 Searched for: (idh1 or ihd2) *phenylsulfonylamino* Results: 0°

Set#: S5 Searched for: (idh1 or ihd2) *sulfon* *urea* Results: 9°

° Duplicates are removed from your search and from your result count.

| | |
|---|---|
| **Electronic Database Searched** | PatBase |
| **Files Searched** | Full-text: AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO<br>Bibliographic: (Europe) AT BA BE BG CH CS CY CZ DD DK EE ES FI GE GR HR HU IE IS IT LT LU LV MC MD MT NL NO PL PT RO RS SE SI SK SM TR UA YU (Asia) EA GC HK ID IL IN KZ MN MY PH RU SG SU TH TJ TW UZ VN (North America) CA CR CU DO GT HN MX NI PA SV TT (South America) AR BR CL CO EC PE UY (Australasia) AU NZ (Africa) AP DZ EG KE MA MW OA ZA ZM ZW |
| **Date Conducted** | 29 January 2014 (29.01.2014) - 04 February 2014 (04.02.2014) |

**Search Logic:**

1) IC=(A61K31/17 or A61K31/18 ) (12871)
2) UC=(514/595 or 514/601 or 514/602 or 514/588 or 514/593 or 514/596 or 514/604) (2093)
3) (1 or 2) and lpr<20121015 (13082)
4) 3 and (idh1 or idh2 or (isocitrate dehydrogenase)) (6)
5) (idh1 or idh2 or (isocitrate dehydrogenase)) (2078)
6) 5 and ((idh1 or idh2 or (isocitrate dehydrogenase)) w5 inhibit*) (54)
7) 6 and (formula* or structure*) (46)
8) 7 and lpr<20121015 (41)
9) 5 and (*benzenesulfonamide* or *phenylsulfonylamino* or *phenylurea*) (36)
10) 3 and (*benzenesulfonamide* or *phenylsulfonylamino* or *phenylurea*) (1787)
11) 10 and cancer* (719)
12) 11 and *urea* (478)
13) 12 and naph* (417)

1) PN=(US2008045589 OR US2009093526 OR US2011275635) (3)
2) 1 and cancer* (3)
3) 2 and (glioma* or myelodysplastic* or myelogenous* or sarcoma*) (2)
4) (idh1 or idh2) and (*sulfonamide* or *phenylsulfonylamino*) (62)
5) 2 and (myelo*) (2)
6) PN=(WO12009678 OR WO10065491 OR WO10056910 OR US2003109527 OR

US2007249625) (4)
7) 6 and idh* (1)
8) idh1 and idh2 and naph* and myelodysplastic* (10)
9) 8 and lpr<20121015 (10)
10) 9 and r140* (3)
11) 6 and myelo* (1)
12) (*phenylsulfonylamino* or *benzenesulfonamide*) (19233)
13) 12 and (myelo*) (2252)
14) PN=(WO11072174) (1)
15) PN=(WO11050201) (1)
16) PN=(WO11050210) (1)

## SUPPLEMENTAL SEARCH: MSS

| | |
|---|---|
| **Electronic Database Searched** | PubWEST |
| **Files Searched** | PGPB,USPT,USOC,EPAB,JPAB |
| **Date Conducted** | 04 February 2014 (04.02.2014) |

**Search Logic:**

Hide? Set Name Query Hit Count

DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=YES; OP=ADJ
L18 L17 and ($urea with $sulfonamid$).ti,ab,clm. 22
L17 L13 and (sulfonamide or sulphonamide).ti,ab,clm. 111
L15 L13 and (isocitrate adj dehydrogenase) 0
L14 L13 and IDH1 0
L13 L12 and ($urea with $sulfonamid$) 227
L12 L11 and ((cancer or tumor or neoplas$) with (disease or disorder)) 1570
L11 L10 and (sulfonamide or sulphonamide) 4971
L10 (urea or phenylurea or diphenylurea).ti,ab,clm. 62006
L9 L7 and (isocitrate adj dehydrogenase) 0
L8 L7 and IDH1 0
L7 L6 and ($urea with $sulfonamid$) 8
L6 L5 and ((cancer or tumor or neoplas$) with (disease or disorder)) 57
L5 L4 and (sulfonamide or sulphonamide) 173
L4 L3 and (urea or phenylurea or diphenylurea).ti,ab,clm. 1098
L3 L1 or L2 6142
L2 514/588.ccls. or 514/593.ccls. or 514/596.ccls. or 514/604.ccls. 1622
L1 A61K031/17.ipc. or A61K031/18.ipc. or 514/595.ccls. or 514/601.ccls. or 514/602.ccls. 5439

END OF SEARCH HISTORY

SEARCH HISTORY

| | |
|---|---|
| **Electronic Database Searched** | SureChem |
| **Files Searched** | USPat, USApp, EPPat, EPApp, WO/PCT, Medline |
| **Date Conducted** | 04 February 2014 (04.02.2014) |
| **Search Logic:** | |
| C1=CC=C(C(=C1)NC(=O)NC2=C(C=CC(=C2)S(=O)(=O)NC3=CC=CC=C3Cl)Cl)Cl | |
| CC1=C(C=C(C=C1)NC(=O)NC2=CC=CC(=C2)C(F)(F)F)S(=O)(=O)NC3=CC=C(C=C3)Cl | |
| CC1=C(C=C(C=C1)NC(=O)NC2=CC=C(C=C2)Cl)S(=O)(=O)N3CCCCC3 | |

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: Asimina T. Georges Evangelinos
Lando & Anastasi LLP
Riverfront Office Park
One Main Street, Suite 1100
Cambridge, MA 02142
United States of America

# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

| | |
|---|---|
| | Date of mailing *(day/month/year)* 15 JUN 2015 |
| Applicant's or agent's file reference C2081-7070WO | **FOR FURTHER ACTION** See paragraphs 1 and 4 below |
| International application No. PCT/US15/20349 | International filing date *(day/month/year)* 13 March 2015 (13.03.2015) |
| Applicant AGIOS PHARMACEUTICALS, INC | |

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   **Filing of amendments and statement under Article 19:**
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   **When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   **How?** Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   **For more detailed instructions**, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

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

Form PCT/ISA/220 (July 2014)

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference<br>C2081-7070WO | **FOR FURTHER ACTION** | see Form PCT/ISA/220<br>as well as, where applicable, item 5 below. |
|---|---|---|
| International application No.<br>PCT/US15/20349 | International filing date *(day/month/year)*<br>13 March 2015 (13.03.2015) | (Earliest) Priority Date *(day/month/year)*<br>14 March 2014 (14.03.2014) |
| Applicant<br>AGIOS PHARMACEUTICALS, INC | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

PHARMACEUTICAL COMPOSITIONS OF THERAPEUTICALLY ACTIVE COMPOUNDS

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/20349

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/19; C07D 251/18 (2015.01)
CPC - A61K 31/19; C07D 251/18
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 31/19; C07D 251/18 (2015.01)
CPC: A61K 31/19; C07D 251/18

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); ProQuest; Scifinder; Google/Google Scholar; KEYWORDS: cancer, tumor, mutant, allele, IDH1, glioma, IHCC, chondrosarcoma, prostate, colon, crystalline, cellulose, polymer, MRI, MRS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>--<br>Y | US 2013/0190249 A1 (AGIOS PHARMACEUTICALS, INC.) 25 July 2013; enparagraphs [0008], [0015], [0094], [0098]-[0099], [0107], [0111]-[0112], [0124], [0134], [0369]-[0372] | 1-3, 25-35, 37-39<br>--<br>4-24, 36 |
| Y | US 2011/0086088 A1 (BERRY, DW) 14 April 2011; paragraphs [0049], [0069], [0073] | 4-20 |
| Y | WO 2014/015422 A1 (ONTARIO INSTITUTE FOR CANCER RESEARCH) 30 January 2014; page 11, paragraph [3]; page 45; paragraph [1] | 21-24 |
| Y | US 2013/0109643 A1 (RIGGINS, GJ et al.) 02 May 2013; paragraphs [0059], [0079] | 36 |
| A | US 2012/0238576 A1 (TAO, C et al.) 20 September 2012, entire document | 1-39 |
| A | US 2010/0273808 A1 (ARMITAGE, I et al.) 28 October 2010; entire document | 1-39 |
| A | US 2012/0121515 A1 (DANG, L et al.) 17 May 2012; entire document | 1-39 |
| A | US 2013/0190287 A1 (AGIOS PHARMACEUTICALS, INC.) 25 July 2013, entire document | 1-39 |
| A | US 2012/0129865 A1 (WANG, B et al.) 24 May 2012; entire document | 1-39 |

☐ 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 |
|---|---|
| 05 May 2015 (05.05.2015) | 15 JUN 2015 |
| Name and mailing address of the ISA/<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer<br>Shane Thomas<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

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

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Asimina T. Georges Evangelinos
Lando & Anastasi LLP
Riverfront Office Park
One Main Street, Suite 1100
Cambridge, MA 02142
United States of America

# PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 15 JUN 2015 |
| Applicant's or agent's file reference<br>C2081-7070WO | FOR FURTHER ACTION<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US15/20349 | 13 March 2015 (13.03.2015) | 14 March 2014 (14.03.2014) |

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/19; C07D 251/18 (2015.01)
CPC - A61K 31/19; C07D 251/18

Applicant AGIOS PHARMACEUTICALS, INC

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

| Name and mailing address of the ISA/ | Date of completion of this opinion | Authorized officer |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | 05 May 2015 (05.05.2015) | Shane Thomas<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/237 (cover sheet) (January 2015)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US15/20349

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US15/20349

**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 4-24, 36 | YES |
| | Claims | 1-3, 25-35, 37-39 | NO |
| Inventive step (IS) | Claims | NONE | YES |
| | Claims | 1-39 | NO |
| Industrial applicability (IA) | Claims | 1-39 | YES |
| | Claims | NONE | NO |

2. Citations and explanations:

Claims 1-3, 25-35 and 37-39 lack novelty under PCT Article 33(2) as being anticipated by US 2013/0190249 A1 to Agios Pharmaceuticals, Inc. (hereinafter 'Agios').

Regarding Claim 1, Agios discloses a method of treating advanced hematologic malignancies in a subject (method of treating cancer (solid tumors) in a subject; paragraph [0008]), each characterized by the presence of a mutant allele of IDH1 (method of treating a cancer characterized by the presence of a mutant allele of IDH1; paragraph [0008]), the method comprising administering to the subject in need thereof a pharmaceutical composition (administering to a subject in need thereof a composition; paragraphs [0008], [0015]) comprising: (a) a compound (S)-N-((S)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl) amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide (Compound 1) (compound of (S)-N-((S)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl) amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide; paragraph [0369]-[0372]), or a pharmaceutically acceptable salt thereof (or pharmaceutically acceptable salt thereof; paragraph [0008]), as part of a solid dispersion (compositions are in the form of dispersion; paragraph [0099]); Form 1 of the Compound 1; or Form 2 of the Compound 1 (compound is racemic mixture Form 1 or Form 2); paragraphs [0369]-[0370]); and optionally (b) one or more pharmaceutically acceptable carriers (composition together with pharmaceutically acceptable carrier; paragraph [0094]).

Regarding Claim 2, Agios discloses the method of claim 1, and Agios further discloses wherein the advanced hematologic malignancies is selected from acute myelogenous leukemia (method of treating acute myelogenous leukemia; paragraphs [0119], [0134]).

Regarding Claim 3, Agios discloses the method of claim 1, and Agios further discloses wherein at least a particular percentage by weight of Compound 1 is crystalline (composition is in the form of a solid (crystalline); paragraph [0098]).

Regarding Claim 25, Agios discloses the method of claim 1, and Agios further discloses wherein the subject is evaluated prior to and/or after treatment with the pharmaceutical composition (levels of 2HG in subject are measured (evaluated) prior to treatment with compound; paragraph [0111]) comprising: (a) Compound 1 (compound of (S)-N-((S)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl) amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide (Compound 1); paragraph [0369]-[0372]) or a pharmaceutically acceptable salt thereof (or pharmaceutically acceptable salt thereof; paragraph [0008]), as part of a solid dispersion (compositions are in the form of dispersion; paragraph [0099]); Form 1 of the Compound 1; or Form 2 of the Compound 1 (compound is racemic mixture Form 1 or Form 2); paragraphs [0369]-[0370]); and optionally (b) one or more pharmaceutically acceptable carriers (composition together with pharmaceutically acceptable carrier; paragraph [0094]), wherein the method comprises determining the 2HG level in the subject (efficacy of treatment is monitored by measuring (determining( the levels of 2HG in the subject; paragraph [0111]).

Regarding Claim 26, Agios discloses the method of claim 25, and Agios further discloses wherein the 2HG level is determined by spectroscopic analysis (LC-MS (spectroscopic analysis) is used to assess 2HG levels; paragraph [0112]).

Regarding Claim 27, Agios discloses the method of claim 26, and Agios further discloses wherein the spectroscopic analysis comprises magnetic resonance-based analysis (2HG levels are measured with MRI and/or MRS (magnetic resonance-based analysis); paragraph [0124]).

Regarding Claim 28, Agios discloses the method of claim 26, and Agios further discloses wherein the spectroscopic analysis comprises MRI and/or MRS measurement (2HG levels are measured with MRI and/or MRS; paragraph [0124]); sample analysis of bodily fluid (sample analysis of bodily fluids; paragraph [0124]); or by analysis of surgical material (analysis of surgical material; paragraph [0124]).

Regarding Claim 29, Agios discloses the method of claim 28, and Agios further discloses wherein the bodily fluid comprises spinal cord fluid (bodily fluid comprises spinal cord fluid; paragraph [0124]).

Regarding Claim 30, Agios discloses the method of claim 28, and Agios further discloses wherein the surgical material is analyzed by mass-spectroscopy (surgical material is analyzed by mass-spectroscopy; paragraph [0124]).

Regarding Claim 31, Agios discloses the method of claim 30, and Agios further discloses wherein the mass-spectroscopy comprises LC-MS or GC-MS (LC-MS is used to assess 2HG levels; paragraph [0112]).

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

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

-***-Continued from Box V: Citations and Explanations-***-

Regarding Claim 32, Agios discloses the method of claim 1, and Agios further discloses wherein the advanced hematologic malignancies are characterized by a mutant allele of IDH1 (cancer characterized by the presence of a mutant allele of IDH1; paragraph [0008]), wherein the IDH1 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of alpha-ketoglutarate to R (-)-2-hydroxyglutarate (2HG) in a patient (mutations of IDH1 present in the cancer cells result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of alpha-ketoglutarate to 2HG; paragraph [0107]).

Regarding Claim 33, Agios discloses the method of claim 32, and Agios further discloses wherein the mutant IDH1 has an R132X mutation (mutant IDH1 has R132X mutation; paragraph [0107]).

Regarding Claim 34, Agios discloses the method of claim 33, and Agios further discloses wherein the R132X mutation is selected from R132H, R132C, R132L, R132V, R132S and R132G (mutant IDH1 has R132X mutation selected from R132H, R132C, R132L, R132V, R132S and R132G; paragraph [0107]).

Regarding Claim 35, Agios discloses the method of claim 33, and Agios further discloses wherein the R132X mutation is R132H or R132C (mutant IDH1 has R132X mutation selected from R132H or R132C; paragraph [0107]).

Regarding Claim 37, Agios discloses the method of claim 1, and Agios further discloses wherein the method comprises administering to the subject in need thereof a pharmaceutical composition comprising Compound 1 (method of administering to a subject in need thereof a pharmaceutical composition; paragraphs [0008], [0015]), or a pharmaceutically acceptable salt thereof (or pharmaceutically acceptable salt thereof; paragraph [0008]), as part of a solid dispersion (compositions are in the form of dispersion; paragraph [0099]).

Regarding Claim 38, Agios discloses the method of claim 1, and Agios further discloses wherein the method comprises administering to the subject in need thereof Form 1 of the Compound 1 (method of administering to a subject in need thereof a pharmaceutical composition containing (S)-N-((S)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)
amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide (Form 1 of the Compound 1); paragraphs [0008], [0015], [0369]).

Regarding Claim 39, Agios discloses the method of claim 1, and Agios further discloses wherein the method comprises administering to the subject in need thereof Form 2 of the Compound 1 (method of administering to a subject in need thereof a pharmaceutical composition containing (S)-N-((S)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)
amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide (Form 1 of the Compound 1); paragraphs [0008], [0015], [0369]).

Claims 4-20 lack an inventive step under PCT Article 33(3) as being obvious over Agios in view of US 2011/0086088 A1 (BERRY).

Regarding Claim 4, Agios discloses the method of claim 3, but Agios does not disclose wherein the particular weight percentage of Compound 1 is 10 percent, 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 75 percent, 80 percent, 85 percent, 87 percent, 88 percent, 89 percent, 90 percent, 91 percent, 92 percent, 93 percent, 94 percent, 95 percent, 96 percent, 97 percent, 98 percent, 99 percent, 99.5 percent, or 99.9 percent. However, Berry discloses wherein the particular weight percentage of Compound 1 is 10 percent, 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 75 percent, 80 percent, 85 percent, 87 percent, 88 percent, 89 percent, 90 percent, 91 percent, 92 percent, 93 percent, 94 percent, 95 percent, 96 percent, 97 percent, 98 percent, 99 percent, 99.5 percent, or 99.9 percent (weight percent crystalline is between 10 and 99.9 percent; paragraph [0049]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the particular weight percentage of Compound 1 is 10 percent, 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 75 percent, 80 percent, 85 percent, 87 percent, 88 percent, 89 percent, 90 percent, 91 percent, 92 percent, 93 percent, 94 percent, 95 percent, 96 percent, 97 percent, 98 percent, 99 percent, 99.5 percent, or 99.9 percent, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 5, Agios and Berry, in combination, disclose the method of claim 3, but Agios does not disclose wherein the particular weight percentage of Compound 1 is between 10 percent and 100 percent. However, Berry discloses wherein the particular weight percentage of Compound 1 is between 10 percent and 100 percent (weight percent crystalline is between 10 and 100 percent; paragraph [0049]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the particular weight percentage of Compound 1 is between 10 percent and 100 percent, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 6, Agios discloses the method of claim 1, but Agios does not disclose wherein a particular percentage by weight of Compound 1 is crystalline, and the remainder of Compound 1 is the amorphous form of Compound 1. However, Berry discloses wherein a particular percentage by weight of Compound 1 is crystalline (part of compound is in crystalline form; paragraph [0069]), and the remainder of Compound 1 is the amorphous form of Compound 1 (part of compound is in amorphous form; paragraph [0069]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein a particular percentage by weight of Compound 1 is crystalline, and the remainder of Compound 1 is the amorphous form of Compound 1, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

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

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

-***-Continued from Previous Supplemental Box-***-

Regarding Claim 7, Agios discloses the method of claim 1, but Agios does not disclose wherein Compound 1 comprises a single crystalline form of Compound 1 or a mixture of different single crystalline forms. However, Berry discloses wherein Compound 1 comprises a single crystalline form of Compound 1 or a mixture of different single crystalline forms (composition is a mixture of different crystalline forms; paragraph [0069]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Compound 1 comprises a single crystalline form of Compound 1 or a mixture of different single crystalline forms, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 8, Agios discloses the method of claim 1, but Agios does not disclose wherein Compound 1 is at least 90 percent by weight crystalline. However, Berry discloses wherein Compound 1 is at least 90 percent by weight crystalline (weight percent crystalline is between 10 and 100 percent; paragraph [0049]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Compound 1 is at least 90 percent by weight crystalline, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 9, Agios discloses the method of claim 1, but Agios does not disclose wherein Compound 1 is at least 95 percent by weight crystalline. However, Berry discloses wherein Compound 1 is at least 95 percent by weight crystalline (weight percent crystalline is between 10 and 100 percent; paragraph [0049]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Compound 1 is at least 95 percent by weight crystalline, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 10, Agios discloses the method of claim 1, but Agios does not disclose wherein Compound 1 is at least 99 percent by weight crystalline. However, Berry discloses wherein Compound 1 is at least 99 percent by weight crystalline (weight percent crystalline is between 10 and 100 percent; paragraph [0049]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Compound 1 is at least 99 percent by weight crystalline, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 11, Agios discloses the method of claim 1, but Agios does not disclose wherein Form 1 of Compound 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 1, and the data shown in Table 1. However, Berry discloses wherein Form 1 of Compound 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 1, and the data shown in Table 1 (XRPD values of 8.27 (8.6), 13.70 (13.2), 15.65 (15.6), 19.65 (19.6), 21.02 (20.6), 21.83 (21.6); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 1 of Compound 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 1, and the data shown in Table 1, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 12, Agios and Berry, in combination, disclose the method of claim 11, but Agios does not disclose wherein the single crystalline form is characterized by one or more of the peaks shown in FIG. 1, and as shown in Table 1. However, Berry discloses wherein the single crystalline form is characterized by one or more of the peaks shown in FIG. 1, and as shown in Table 1 (XRPD value of 15.65 (15.6); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the single crystalline form is characterized by one or more of the peaks shown in FIG. 1, and as shown in Table 1, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 13, Agios and Berry, in combination, disclose the method of claim 11, but Agios does not disclose wherein the single crystalline form is characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 1. However, Berry discloses wherein the single crystalline form is characterized by one of the peaks shown in Table 1 (XRPD value of 15.65 (15.6); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the single crystalline form is characterized by one of the peaks shown in Table 1, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 14, Agios and Berry, in combination, disclose the method of claim 11, but Agios does not disclose wherein Form 1 is characterized by the peaks identified at 2-theta angles of 8.6, 15.6, 18.5, 20.6, 21.6, and 26.4 degrees. However, Berry discloses wherein Form 1 is characterized by the peaks identified at 2-theta angles of 8.6, 15.6, 20.6 and 21.6 degrees (XRPD values of 8.27 (8.6), 15.65 (15.6), 21.02 (20.6), 21.83 (21.6); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 1 is characterized by the peaks identified at 2-theta angles of 8.6, 15.6, 20.6 and 21.6 degrees, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

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

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

-***-Continued from Previous Supplemental Box-***-

Regarding Claim 15, Agios and Berry, in combination, disclose the method of claim 11, but Agios does not disclose wherein Form 1 is characterized by the peaks identified at 2-theta angles of 8.6, 15.6, 18.5, and 21.6 degrees. However, Berry discloses wherein Form 1 is characterized by the peaks identified at 2-theta angles of 8.6, 15.6 and 21.6 degrees (XRPD values of 8.27 (8.6), 15.65 (15.6) and 21.83 (21.6); paragraph [0073]) It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 1 is characterized by the peaks identified at 2-theta angles of 8.6, 15.6 and 21.6 degrees, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 16, Agios discloses the method of claim 1, but Agios does not disclose wherein Form 2 of the Compound 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 4, and the data shown in Table 2. However, Berry discloses wherein Form 2 of the Compound 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 4, and the data shown in Table 2 (XRPD values of 9.99 (9.8), 12.11 (11.6), 15.09 (14.9), 16.52 (16.5), 19.65 (19.6), 19.97 (20.1) and 22.32 (22.5); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 2 of the Compound 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 4, and the data shown in Table 2, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 17, Agios and Berry, in combination, disclose the method of claim 16, but Agios does not disclose wherein Form 2 is characterized by one or more of the peaks shown in FIG. 4, and as shown in Table 2. However, Berry discloses wherein Form 2 is characterized by one or more of the peaks shown in FIG. 4, and as shown in Table 2 (XRPD value of 16.52 (16.5); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 2 is characterized by one or more of the peaks shown in FIG. 4, and as shown in Table 2, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 18, Agios and Berry, in combination, disclose the method of claim 16, but Agios does not disclose wherein Form 2 is characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 2. However, Berry discloses wherein Form 2 is characterized by one of the peaks shown in Table 2 (XRPD value of 16.52 (16.5); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 2 is characterized by one of the peaks shown in Table 2, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 19, Agios and Berry, in combination, disclose the method of claim 16, but Agios does not disclose wherein Form 2 is characterized by the peaks identified at 2-theta angles of 9.8, 11.6, 19.6, 22.5, 23.0, and 31.4 degrees. However, Berry discloses wherein Form 2 is characterized by the peaks identified at 2-theta angles of 9.8, 11.6, 19.6 and 22.5 degrees (XRPD values of 9.99 (9.8), 12.11 (11.6), 19.65 (19.6) and 22.32 (22.5); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 2 is characterized by the peaks identified at 2-theta angles of 9.8, 11.6, 19.6 and 22.5 degrees, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 20, Agios and Berry, in combination, disclose the method of claim 11, but Agios does not disclose wherein Form 2 is characterized by the peaks identified at 2-theta angles of 9.8, 11.6, 19.6, and 23.0 degrees. However, Berry discloses wherein Form 2 is characterized by the peaks identified at 2-theta angles of 9.8, 11.6 and 19.6 (XRPD values of 9.99 (9.8), 12.11 (11.6) and 19.65 (19.6); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 2 is characterized by the peaks identified at 2-theta angles of 9.8, 11.6 and 19.6, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Claims 21-24 lack an inventive step under PCT Article 33(3) as being obvious over Agios in view of WO 2014/015422 A1 to Ontario Institute for Cancer Research (hereinafter 'Ontario').

Regarding Claim 21, Agios discloses the method of claim 1, but Agios does not disclose wherein the solid dispersion comprises a water-soluble polymer. However, Ontario discloses wherein the solid dispersion comprises a water-soluble polymer (dispersion is an aqueous (water-soluble), cellulose-based (polymer) composition; page 11, paragraph [3]; page 45, paragraph [1]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the solid dispersion comprises a water-soluble polymer, as previously disclosed by Ontario, for providing a pharmaceutical composition with varying reactivity of the carboxylic acid groups.

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

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US15/20349

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

-***-Continued from Previous Supplemental Box-***-

Regarding Claim 22, Agios discloses the method of claim 1, but Agios does not disclose wherein the solid dispersion comprises one partially water-soluble polymer. However, Ontario discloses wherein the solid dispersion comprises one partially water-soluble polymer (polymer is partially water soluble; page 45, paragraph [1]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the solid dispersion comprises one partially water-soluble polymer, as previously disclosed by Ontario, for providing a pharmaceutical composition with varying reactivity of the carboxylic acid groups.

Regarding Claim 23, Agios and Ontario, in combination, disclose the method of claim 21, but Agios does not disclose wherein the polymer is a cellulose polymer. However, Ontario discloses wherein the polymer is a cellulose polymer (dispersion is an aqueous (water-soluble), cellulose-based (polymer) composition; page 11, paragraph [3]; page 45, paragraph [1]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the polymer is a cellulose polymer, as previously disclosed by Ontario, for providing a pharmaceutical composition with varying reactivity of the carboxylic acid groups.

Regarding Claim 24, Agios and Ontario, in combination, disclose the method of claim 21, and Agios further discloses wherein the efficacy of treatment of advanced solid tumors is monitored by measuring the levels of 2HG in the subject (efficacy of cancer (solid tumors) treatment is monitored by measuring the levels of 2HG in the subject; paragraph [0111]).

Claim 36 lacks an inventive step under PCT Article 33(3) as being obvious over Agios in view of US 2013/0109643 A1 to Riggins, et al. (hereinafter 'Riggins').

Regarding Claim 36, Agios discloses the method of claim 1, but Agios does not disclose wherein the advanced hematologic malignancies are characterized by a co-mutation selected from NPM1, FLT3, TET2, CEBPA, DNMT3A, and MLL. However, Riggins discloses wherein the advanced hematologic malignancies are characterized by a co-mutation selected from NPM1 and FLT3 (cancer (hematologic malignancy) has mutant of NPM-1 and FLT3; paragraphs [0059], [0079]). It would have been obvious to a person of ordinary skill in the art at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the advanced hematologic malignancies are characterized by a co-mutation selected from NPM1 and FLT3, as previously disclosed by Riggins, for providing an effective pharmaceutical to inhibit glutaminase for use in cancer therapy.

Claims 1-39 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

# PCT Recordation of Search History

Case/PCT Application Number: PCT/US15/20349

CLIN Number/Technical Field of PCT Application: 8

Date(s) During Which the Search was Conducted: 04 May 2015 – 05 May 2015

Date of Completion of Recordation of Search History Form: 05 May 2015

Research Analyst Initials: KAC

Search Approval Official (SAO) Initials: DEF

**Field of Search/Classification Information:**

IPC(8) Classification(s): A61K 31/19; C07D 251/18 (2015.01)

CPC Classification(s): A61K 31/19; C07D 251/18

USPC Classification(s) (if searched):

**Database(s) Searched (Patent and Non-Patent Literature (NPL), Including Sub-Databases and Files Searched) and Search Terms Used:**

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); ProQuest; Scifinder; Google/Google Scholar; KEYWORDS: cancer, tumor, mutant, allele, IDH1, glioma, IHCC, chondrosarcoma, prostate, colon, crystalline, cellulose, polymer, MRI, MRS

**Database Search String Recordation, Including Dates of Searches):**

| ID | Term | Date | Count |
|---|---|---|---|
| L31 | CPC:(A61K31/19*) | 05-May-2015 | 81965 |
| L30 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND CPC:(A61K31/19*) | 05-May-2015 | 3 |
| L29 | CPC:(C07D251/18*) | 05-May-2015 | 2299 |
| L28 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND CPC:(C07D251/18*) | 05-May-2015 | 1 |
| L27 | IC:(C07D251/18*) | 05-May-2015 | 4152 |
| L26 | TAC:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND IC:(C07D251/18*) | 05-May-2015 | 12 |
| L25 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND IC:(C07D251*) | 05-May-2015 | 1 |

| | | | |
|---|---|---|---|
| L24 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND IC:(C07D*) | 05-May-2015 | 17 |
| L23 | IC:(A61K31/19*) | 05-May-2015 | 171388 |
| L22 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND IC:(A61K31/19*) | 05-May-2015 | 1 |
| L21 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND IC:(A61K31*) | 05-May-2015 | 35 |
| L20 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND IC:(A61K*) | 05-May-2015 | 52 |
| L19 | TA:((cancer* OR tumor*)) AND TACD:((polymer* wp solvent* wp (water* w2 soluble) wp dispersion*)) | 05-May-2015 | 426 |
| L18 | TA:((cancer* OR tumor*)) AND TACD:((polymer* wp solvent* wp water* wp dispersion*)) AND ASNN:(agios) | 05-May-2015 | 7 |
| L17 | TA:((cancer* OR tumor*)) AND TACD:((polymer* wp solvent* wp water* wp dispersion*)) | 05-May-2015 | 1869 |
| L16 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND TACD:(polymer* wp solvent* wp water*) | 05-May-2015 | 1 |
| L15 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND TACD:(polymer* wp solvent* wp water* wp solubl*) | 05-May-2015 | 0 |
| L14 | TA:((cancer* OR tumor*)) AND TACD:(crystalline AND (water wp solvent*)) AND TAC:("idh1" OR "idh2") | 05-May-2015 | 8 |
| L13 | TA:((cancer* OR tumor*)) AND TACD:(crystalline AND amorphous* AND (water wp solvent*)) AND TAC:("idh1" OR "idh2") | 05-May-2015 | 1 |
| L12 | TA:((cancer* OR tumor*)) AND TACD:(crystalline AND amorphous* AND (weight wp percent* wp crystal*)) AND TAC:("idh1" OR "idh2" OR glioma OR cholangiocarcin* OR chondrosarcoma* OR prostate* OR colon OR melanoma) | 05-May-2015 | 133 |
| L11 | TA:((cancer* OR tumor*)) AND TACD:(crystalline AND amorphous* AND (weight wp percent* wp crystal*)) AND TAC:("idh1" OR "idh2") | 05-May-2015 | 1 |
| L10 | TA:((cancer* OR tumor*)) AND TACD:(crystalline AND amorphous* AND (weight wp percent* wp crystal*)) | 05-May-2015 | 334 |
| L9 | TA:((cancer* OR tumor*)) AND TACD:(crystalline AND amorphous* AND (weight wp percent*)) | 05-May-2015 | 3586 |
| L8 | TAC:("idh1" AND (cancer* OR tumor*)) AND TACD:(crystalline AND amorphous*) | 05-May-2015 | 1 |
| L7 | TAC:(("idh1" AND (cancer* OR tumor*)) AND (crystalline AND amorphous*)) | 05-May-2015 | 0 |
| L6 | TAC:(crystal* AND "idh1") | 05-May-2015 | 12 |
| L5 | TAC:(crystal* AND amorph*) AND ASNN:(agios) | 05-May-2015 | 0 |
| L4 | TAC:(crystal*) AND ASNN:(AGIOS) | 04-May-2015 | 3 |
| L3 | TAC:(tumor*) AND ASNN:(AGIOS) | 04-May-2015 | 18 |
| L2 | TA:(tumor*) AND ASNN:(AGIOS) | 04-May-2015 | 0 |
| L1 | ASNN:(AGIOS) | 04-May-2015 | 268 |

**Patent Database Search Strategy/Results:**

**Non-Patent Literature (NPL) Search Strategy/Results:**

[redacted]

**Google Scholar:**

**05 May 2015:**

| | |
|---|---|
| cancer tumor allele IDH1 | 3700 |
| cancer tumor allele IDH1 chondrosarcoma | 224 |
| cancer tumor allele IDH1 glioma | 2300 |
| cancer tumor allele IDH1 glioma cellulose polymer | 51 |
| cancer tumor allele IDH1 glioma cellulose polymer MRI | 17 |

**ProQuest:**

**05 May 2015:**

| | |
|---|---|
| allele AND IDH1 | 123 |
| allele AND IDH1 AND cellulose | 1 |
| allele AND IDH1 AND polymer | 0 |

**EBSCO:**

**05 May 2015:**

| | |
|---|---|
| allele AND IDH1 | 5581 |
| allele AND IDH1 AND cellulose | 542 |
| allele AND IDH1 AND cellulose AND polymer | 206 |

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: Asimina T. Georges Evangelinos
Lando & Anastasi LLP
Riverfront Office Park
One Main Street, Suite 1100
Cambridge, MA 02142
United States of America

# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

| | |
|---|---|
| | Date of mailing *(day/month/year)* 18 JUN 2015 |
| Applicant's or agent's file reference C2081-7069WO | **FOR FURTHER ACTION** See paragraphs 1 and 4 below |
| International application No. PCT/US15/20346 | International filing date *(day/month/year)* 13 March 2015 (13.03.2015) |
| Applicant AGIOS PHARMACEUTICALS, INC | |

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   **Filing of amendments and statement under Article 19:**
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   **When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   **How?** Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   **For more detailed instructions**, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   - ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

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

Form PCT/ISA/220 (July 2014)

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference C2081-7069WO | FOR FURTHER ACTION | see Form PCT/ISA/220 as well as, where applicable, item 5 below. |
|---|---|---|
| International application No. PCT/US15/20346 | International filing date *(day/month/year)* 13 March 2015 (13.03.2015) | (Earliest) Priority Date *(day/month/year)* 14 March 2014 (14.03.2014) |
| Applicant AGIOS PHARMACEUTICALS, INC | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

PHARMACEUTICAL COMPOSITIONS OF THERAPEUTICALLY ACTIVE COMPOUNDS

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/20346

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/19; C07D 251/18 (2015.01)
CPC - A61K 31/19; C07D 251/18
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 31/19; C07D 251/18 (2015.01)
CPC: A61K 31/19; C07D 251/18

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); ProQuest; Scifinder; Google/Google Scholar; KEYWORDS: cancer, tumor, mutant, allele, IDH1, glioma, IHCC, chondrosarcoma, prostate, colon, crystalline, cellulose, polymer, MRI, MRS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>--<br>Y | US 2013/0190249 A1 (AGIOS PHARMACEUTICALS, INC.) 25 July 2013; enparagraphs [0008], [0015], [0094], [0098]-[0099], [0107], [0111]-[0112], [0124], [0134], [0369]-[0372] | 1-3, 25-36<br>----------<br>4-24 |
| Y | US 2011/0086088 A1 (BERRY, DW) 14 April 2011; paragraphs [0049], [0069], [0073] | 4-20 |
| Y | WO 2014/015422 A1 (ONTARIO INSTITUTE FOR CANCER RESEARCH) 30 January 2014; page 11, paragraph [3]; page 45; paragraph [1] | 21-24 |
| A | US 2012/0238576 A1 (TAO, C et al.) 20 September 2012; entire document | 1-38 |
| A | US 2010/0273808 A1 (ARMITAGE, I et al.) 28 October 2010; entire document | 1-38 |
| A | US 2012/0121515 A1 (DANG, L et al.) 17 May 2012; entire document | 1-38 |
| A | US 2013/0190287 A1 (AGIOS PHARMACEUTICALS, INC.) 25 July 2013; entire document | 1-38 |
| A | US 2012/0129865 A1 (WANG, B et al.) 24 May 2012; entire document | 1-38 |

☐ 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 |
|---|---|
| 05 May 2015 (05.05.2015) | 18 JUN 2015 |
| Name and mailing address of the ISA/<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer<br>Shane Thomas<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

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

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Asimina T. Georges Evangelinos
Lando & Anastasi LLP
Riverfront Office Park
One Main Street, Suite 1100
Cambridge, MA 02142
United States of America

**PCT**

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 18 JUN 2015 |
| Applicant's or agent's file reference<br>C2081-7069WO | **FOR FURTHER ACTION**<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US15/20346 | 13 March 2015 (13.03.2015) | 14 March 2014 (14.03.2014) |

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/19; C07D 251/18 (2015.01)
CPC - A61K 31/19; C07D 251/18

Applicant AGIOS PHARMACEUTICALS, INC

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

| Name and mailing address of the ISA/ | Date of completion of this opinion | Authorized officer |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | 05 May 2015 (05.05.2015) | Shane Thomas<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/237 (cover sheet) (January 2015)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US15/20346

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US15/20346

**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 4-24 | YES |
| | Claims | 1-3, 25-38 | NO |
| Inventive step (IS) | Claims | NONE | YES |
| | Claims | 1-38 | NO |
| Industrial applicability (IA) | Claims | 1-38 | YES |
| | Claims | NONE | NO |

2. Citations and explanations:

Claims 1-3 and 25-38 lack novelty under PCT Article 33(2) as being anticipated by US 2013/0190249 A1 to Agios Pharmaceuticals, Inc. (hereinafter 'Agios').

Regarding Claim 1, Agios discloses a method of treating advanced solid tumors in a subject (method of treating cancer (solid tumors) in a subject; paragraph [0008]), each characterized by the presence of a mutant allele of IDH1 (method of treating a cancer characterized by the presence of a mutant allele of IDH1; paragraph [0008]), the method comprising administering to the subject in need thereof a pharmaceutical composition (administering to a subject in need thereof a composition; paragraphs [0008], [0015]) comprising: (a) a compound (S)-N-((S)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl) amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide (Compound 1) (compound of (S)-N-((S)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl) amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide; paragraph [0369]-[0372]), or a pharmaceutically acceptable salt thereof (or pharmaceutically acceptable salt thereof; paragraph [0008]), as part of a solid dispersion (compositions are in the form of dispersion; paragraph [0099]); Form 1 of the Compound 1; or Form 2 of the Compound 1 (compound is racemic mixture Form 1 or Form 2); paragraphs [0369]-[0370]); and optionally (b) one or more pharmaceutically acceptable carriers (composition together with pharmaceutically acceptable carrier; paragraph [0094]).

Regarding Claim 2, Agios discloses the method of claim 1, and Agios further discloses wherein the advanced solid tumors is selected from glioma, chondrosarcoma, prostate cancer, colon cancer, melanoma, and non-small cell lung cancer (NSCLC) (method of treating glioma, chondrosarcoma, prostate cancer, colon cancer, melanoma and NSCLC; paragraphs [0119], [0134]).

Regarding Claim 3, Agios discloses the method of claim 1, and Agios further discloses wherein at least a particular percentage by weight of Compound 1 is crystalline (composition is in the form of a solid (crystalline); paragraph [0098]).

Regarding Claim 25, Agios discloses the method of claim 1, and Agios further discloses wherein the subject is evaluated prior to and/or after treatment with the pharmaceutical composition (levels of 2HG in subject are measured (evaluated) prior to treatment with compound; paragraph [0111]) comprising: (a) Compound 1 (compound of (S)-N-((S)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl) amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide (Compound 1); paragraph [0369]-[0372]) or a pharmaceutically acceptable salt thereof (or pharmaceutically acceptable salt thereof; paragraph [0008]), as part of a solid dispersion (compositions are in the form of dispersion; paragraph [0099]); Form 1 of the Compound 1; or Form 2 of the Compound 1 (compound is racemic mixture Form 1 or Form 2); paragraphs [0369]-[0370]); and optionally (b) one or more pharmaceutically acceptable carriers (composition together with pharmaceutically acceptable carrier; paragraph [0094]), wherein the method comprises determining the 2HG level in the subject (efficacy of treatment is monitored by measuring (determining( the levels of 2HG in the subject; paragraph [0111]).

Regarding Claim 26, Agios discloses the method of claim 25, and Agios further discloses wherein the 2HG level is determined by spectroscopic analysis (LC-MS (spectroscopic analysis) is used to assess 2HG levels; paragraph [0112]).

Regarding Claim 27, Agios discloses the method of claim 26, and Agios further discloses wherein the spectroscopic analysis comprises magnetic resonance-based analysis (2HG levels are measured with MRI and/or MRS (magnetic resonance-based analysis); paragraph [0124]).

Regarding Claim 28, Agios discloses the method of claim 26, and Agios further discloses wherein the spectroscopic analysis comprises MRI and/or MRS measurement (2HG levels are measured with MRI and/or MRS; paragraph [0124]); sample analysis of bodily fluid (sample analysis of bodily fluids; paragraph [0124]); or by analysis of surgical material (analysis of surgical material; paragraph [0124]).

Regarding Claim 29, Agios discloses the method of claim 28, and Agios further discloses wherein the bodily fluid comprises spinal cord fluid (bodily fluid comprises spinal cord fluid; paragraph [0124]).

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

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

-***-Continued from Box V: Citations and Explanations-***-

Regarding Claim 30, Agios discloses the method of claim 28, and Agios further discloses wherein the surgical material is analyzed by mass-spectroscopy (surgical material is analyzed by mass-spectroscopy; paragraph [0124]).

Regarding Claim 31, Agios discloses the method of claim 30, and Agios further discloses wherein the mass-spectroscopy comprises LC-MS or GC-MS (LC-MS is used to assess 2HG levels; paragraph [0112]).

Regarding Claim 32, Agios discloses the method of claim 1, and Agios further discloses wherein the advanced solid tumors are characterized by a mutant allele of IDH1 (cancer characterized by the presence of a mutant allele of IDH1; paragraph [0008]), wherein the IDH1 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of alpha-ketoglutarate to R (-)-2-hydroxyglutarate (2HG) in a patient (mutations of IDH1 present in the cancer cells result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of alpha-ketoglutarate to 2HG; paragraph [0107]).

Regarding Claim 33, Agios discloses the method of claim 32, and Agios further discloses wherein the mutant IDH1 has an R132X mutation (mutant IDH1 has R132X mutation; paragraph [0107]).

Regarding Claim 34, Agios discloses the method of claim 33, and Agios further discloses wherein the R132X mutation is selected from R132H, R132C, R132L, R132V, R132S and R132G (mutant IDH1 has R132X mutation selected from R132H, R132C, R132L, R132V, R132S and R132G; paragraph [0107]).

Regarding Claim 35, Agios discloses the method of claim 33, and Agios further discloses wherein the R132X mutation is R132H or R132C (mutant IDH1 has R132X mutation selected from R132H or R132C; paragraph [0107]).

Regarding Claim 36, Agios discloses the method of claim 1, and Agios further discloses wherein the method comprises administering to the subject in need thereof a pharmaceutical composition comprising Compound 1 (method of administering to a subject in need thereof a pharmaceutical composition; paragraphs [0008], [0015]), or a pharmaceutically acceptable salt thereof (or pharmaceutically acceptable salt thereof; paragraph [0006]), as part of a solid dispersion (compositions are in the form of dispersion; paragraph [0099]).

Regarding Claim 37, Agios discloses the method of claim 1, and Agios further discloses wherein the method comprises administering to the subject in need thereof Form 1 of the Compound 1 (method of administering to a subject in need thereof a pharmaceutical composition containing (S)-N-((S)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)
amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide (Form 1 of the Compound 1); paragraphs [0008], [0015], [0369]).

Regarding Claim 38, Agios discloses the method of claim 1, and Agios further discloses wherein the method comprises administering to the subject in need thereof Form 2 of the Compound 1 (method of administering to a subject in need thereof a pharmaceutical composition containing (S)-N-((S)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)
amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide (Form 1 of the Compound 1); paragraphs [0008], [0015], [0369]).

Claims 4-20 lack an inventive step under PCT Article 33(3) as being obvious over Agios in view of US 2011/0086088 A1 (BERRY).

Regarding Claim 4, Agios discloses the method of claim 3, but Agios does not disclose wherein the particular weight percentage of Compound 1 is 10 percent, 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 75 percent, 80 percent, 85 percent, 87 percent, 88 percent, 89 percent, 90 percent, 91 percent, 92 percent, 93 percent, 94 percent, 95 percent, 96 percent, 97 percent, 98 percent, 99 percent, 99.5 percent, or 99.9 percent. However, Berry discloses wherein the particular weight percentage of Compound 1 is 10 percent, 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 75 percent, 80 percent, 85 percent, 87 percent, 88 percent, 89 percent, 90 percent, 91 percent, 92 percent, 93 percent, 94 percent, 95 percent, 96 percent, 97 percent, 98 percent, 99 percent, 99.5 percent, or 99.9 percent (weight percent crystalline is between 10 and 99.9 percent; paragraph [0049]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the particular weight percentage of Compound 1 is 10 percent, 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 75 percent, 80 percent, 85 percent, 87 percent, 88 percent, 89 percent, 90 percent, 91 percent, 92 percent, 93 percent, 94 percent, 95 percent, 96 percent, 97 percent, 98 percent, 99 percent, 99.5 percent, or 99.9 percent, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 5, Agios and Berry, in combination, disclose the method of claim 3, but Agios does not disclose wherein the particular weight percentage of Compound 1 is between 10 percent and 100 percent. However, Berry discloses wherein the particular weight percentage of Compound 1 is between 10 percent and 100 percent (weight percent crystalline is between 10 and 100 percent; paragraph [0049]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the particular weight percentage of Compound 1 is between 10 percent and 100 percent, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

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

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

-***-Continued from Previous Supplemental Box-***-

Regarding Claim 6, Agios discloses the method of claim 1, but Agios does not disclose wherein a particular percentage by weight of Compound 1 is crystalline, and the remainder of Compound 1 is the amorphous form of Compound 1. However, Berry discloses wherein a particular percentage by weight of Compound 1 is crystalline (part of compound is in crystalline form; paragraph [0069]), and the remainder of Compound 1 is the amorphous form of Compound 1 (part of compound is in amorphous form; paragraph [0069]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein a particular percentage by weight of Compound 1 is crystalline, and the remainder of Compound 1 is the amorphous form of Compound 1, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 7, Agios discloses the method of claim 1, but Agios does not disclose wherein Compound 1 comprises a single crystalline form of Compound 1 or a mixture of different single crystalline forms. However, Berry discloses wherein Compound 1 comprises a single crystalline form of Compound 1 or a mixture of different single crystalline forms (composition is a mixture of different crystalline forms; paragraph [0069]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Compound 1 comprises a single crystalline form of Compound 1 or a mixture of different single crystalline forms, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 8, Agios discloses the method of claim 1, but Agios does not disclose wherein Compound 1 is at least 90 percent by weight crystalline. However, Berry discloses wherein Compound 1 is at least 90 percent by weight crystalline (weight percent crystalline is between 10 and 100 percent; paragraph [0049]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Compound 1 is at least 90 percent by weight crystalline, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 9, Agios discloses the method of claim 1, but Agios does not disclose wherein Compound 1 is at least 95 percent by weight crystalline. However, Berry discloses wherein Compound 1 is at least 95 percent by weight crystalline (weight percent crystalline is between 10 and 100 percent; paragraph [0049]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Compound 1 is at least 95 percent by weight crystalline, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 10, Agios discloses the method of claim 1, but Agios does not disclose wherein Compound 1 is at least 99 percent by weight crystalline. However, Berry discloses wherein Compound 1 is at least 99 percent by weight crystalline (weight percent crystalline is between 10 and 100 percent; paragraph [0049]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Compound 1 is at least 99 percent by weight crystalline, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 11, Agios discloses the method of claim 1, but Agios does not disclose wherein Form 1 of Compound 1 is characterized by the X--ray powder diffraction (XRPD) pattern shown in FIG. 1, and the data shown in Table 1. However, Berry discloses wherein Form 1 of Compound 1 is characterized by the X--ray powder diffraction (XRPD) pattern shown in FIG. 1, and the data shown in Table 1 (XRPD values of 8.27 (8.6), 13.70 (13.2), 15.65 (15.6), 19.65 (19.6), 21.02 (20.6), 21.83 (21.6); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 1 of Compound 1 is characterized by the X--ray powder diffraction (XRPD) pattern shown in FIG. 1, and the data shown in Table 1, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 12, Agios and Berry, in combination, disclose the method of claim 11, but Agios does not disclose wherein the single crystalline form is characterized by one or more of the peaks shown in FIG. 1, and as shown in Table 1. However, Berry discloses wherein the single crystalline form is characterized by one or more of the peaks shown in FIG. 1, and as shown in Table 1 (XRPD value of 15.65 (15.6); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the single crystalline form is characterized by one or more of the peaks shown in FIG. 1, and as shown in Table 1, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

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

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

-***-Continued from Previous Supplemental Box-***-

Regarding Claim 13, Agios and Berry, in combination, disclose the method of claim 11, but Agios does not disclose wherein the single crystalline form is characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 1. However, Berry discloses wherein the single crystalline form is characterized by one of the peaks shown in Table 1 (XRPD value of 15.65 (15.6); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the single crystalline form is characterized by one of the peaks shown in Table 1, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 14, Agios and Berry, in combination, disclose the method of claim 11, but Agios does not disclose wherein Form 1 is characterized by the peaks identified at 2-theta angles of 8.6, 15.6, 18.5, 20.6, 21.6, and 26.4 degrees. However, Berry discloses wherein Form 1 is characterized by the peaks identified at 2-theta angles of 8.6, 15.6, 20.6 and 21.6 degrees (XRPD values of 8.27 (8.6), 15.65 (15.6), 21.02 (20.6), 21.83 (21.6); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 1 is characterized by the peaks identified at 2-theta angles of 8.6, 15.6, 20.6 and 21.6 degrees, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 15, Agios and Berry, in combination, disclose the method of claim 11, but Agios does not disclose wherein Form 1 is characterized by the peaks identified at 2-theta angles of 8.6, 15.6, 18.5, and 21.6 degrees. However, Berry discloses wherein Form 1 is characterized by the peaks identified at 2-theta angles of 8.6, 15.6 and 21.6 degrees (XRPD values of 8.27 (8.6), 15.65 (15.6) and 21.83 (21.6); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 1 is characterized by the peaks identified at 2-theta angles of 8.6, 15.6 and 21.6 degrees, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 16, Agios discloses the method of claim 1, but Agios does not disclose wherein Form 2 of the Compound 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 4, and the data shown in Table 2. However, Berry discloses wherein Form 2 of the Compound 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 4, and the data shown in Table 2 (XRPD values of 9.99 (9.8), 12.11 (11.6), 15.09 (14.9), 16.52 (16.5), 19.65 (19.6), 19.97 (20.1) and 22.32 (22.5); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 2 of the Compound 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 4, and the data shown in Table 2, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 17, Agios and Berry, in combination, disclose the method of claim 16, but Agios does not disclose wherein Form 2 is characterized by one or more of the peaks shown in FIG. 4, and as shown in Table 2. However, Berry discloses wherein Form 2 is characterized by one or more of the peaks shown in FIG. 4, and as shown in Table 2 (XRPD value of 16.52 (16.5); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 2 is characterized by one or more of the peaks shown in FIG. 4, and as shown in Table 2, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 18, Agios and Berry, in combination, disclose the method of claim 16, but Agios does not disclose wherein Form 2 is characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 2. However, Berry discloses wherein Form 2 is characterized by one of the peaks shown in Table 2 (XRPD value of 16.52 (16.5); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 2 is characterized by one of the peaks shown in Table 2, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 19, Agios and Berry, in combination, disclose the method of claim 16, but Agios does not disclose wherein Form 2 is characterized by the peaks identified at 2-theta angles of 9.8, 11.6, 19.6, 22.5, 23.0, and 31.4 degrees. However, Berry discloses wherein Form 2 is characterized by the peaks identified at 2-theta angles of 9.8, 11.6, 19.6 and 22.5 degrees (XRPD values of 9.99 (9.8), 12.11 (11.6), 19.65 (19.6) and 22.32 (22.5); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 2 is characterized by the peaks identified at 2-theta angles of 9.8, 11.6, 19.6 and 22.5 degrees, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

Regarding Claim 20, Agios and Berry, in combination, disclose the method of claim 11, but Agios does not disclose wherein Form 2 is characterized by the peaks identified at 2-theta angles of 9.8, 11.6, 19.6, and 23.0 degrees. However, Berry discloses wherein Form 2 is characterized by the peaks identified at 2-theta angles of 9.8, 11.6 and 19.6 (XRPD values of 9.99 (9.8), 12.11 (11.6) and 19.65 (19.6); paragraph [0073]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein Form 2 is characterized by the peaks identified at 2-theta angles of 9.8, 11.6 and 19.6, as previously disclosed by Berry, for providing a pharmaceutical composition for treating disorders such as melanoma (Berry; paragraph [0004]).

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

**Supplemental Box**

**In case the space in any of the preceding boxes is not sufficient.**
Continuation of:

-***-Continued from Previous Supplemental Box-***-

Claims 21-24 lack an inventive step under PCT Article 33(3) as being obvious over Agios in view of WO 2014/015422 A1 to Ontario Institute for Cancer Research (hereinafter 'Ontario').

Regarding Claim 21, Agios discloses the method of claim 1, but Agios does not disclose wherein the solid dispersion comprises a water-soluble polymer. However, Ontario discloses wherein the solid dispersion comprises a water-soluble polymer (dispersion is an aqueous (water-soluble), cellulose-based (polymer) composition; page 11, paragraph [3]; page 45, paragraph [1]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the solid dispersion comprises a water-soluble polymer, as previously disclosed by Ontario, for providing a pharmaceutical composition with varying reactivity of the carboxylic acid groups.

Regarding Claim 22, Agios discloses the method of claim 1, but Agios does not disclose wherein the solid dispersion comprises one partially water-soluble polymer. However, Ontario discloses wherein the solid dispersion comprises one partially water-soluble polymer (polymer is partially water soluble; page 45, paragraph [1]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the solid dispersion comprises one partially water-soluble polymer, as previously disclosed by Ontario, for providing a pharmaceutical composition with varying reactivity of the carboxylic acid groups.

Regarding Claim 23, Agios and Ontario, in combination, disclose the method of claim 21, but Agios does not disclose wherein the polymer is a cellulose polymer. However, Ontario discloses wherein the polymer is a cellulose polymer (dispersion is an aqueous (water-soluble), cellulose-based (polymer) composition; page 11, paragraph [3]; page 45, paragraph [1]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by Agios, in order to have provided wherein the polymer is a cellulose polymer, as previously disclosed by Ontario, for providing a pharmaceutical composition with varying reactivity of the carboxylic acid groups.

Regarding Claim 24, Agios and Ontario, in combination, disclose the method of claim 21, and Agios further discloses wherein the efficacy of treatment of advanced solid tumors is monitored by measuring the levels of 2HG in the subject (efficacy of cancer (solid tumors) treatment is monitored by measuring the levels of 2HG in the subject; paragraph [0111]).

Claims 1-36 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

# PCT Recordation of Search History

Case/PCT Application Number: PCT/US15/20346

CLIN Number/Technical Field of PCT Application: 8

Date(s) During Which the Search was Conducted: 04 May 2015 – 05 May 2015

Date of Completion of Recordation of Search History Form: 05 May 2015

Research Analyst Initials: KAC

Search Approval Official (SAO) Initials: DEF

**Field of Search/Classification Information:**

IPC(8) Classification(s): A61K 31/19; C07D 251/18 (2015.01)

CPC Classification(s): A61K 31/19; C07D 251/18

USPC Classification(s) (if searched):

**Database(s) Searched (Patent and Non-Patent Literature (NPL), Including Sub-Databases and Files Searched) and Search Terms Used:**

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); ProQuest; Scifinder; Google/Google Scholar; KEYWORDS: cancer, tumor, mutant, allele, IDH1, glioma, IHCC, chondrosarcoma, prostate, colon, crystalline, cellulose, polymer, MRI, MRS

**Database Search String Recordation, Including Dates of Searches):**

| ID | Term | Date | Count |
|---|---|---|---|
| L31 | CPC:(A61K31/19*) | 05-May-2015 | 81965 |
| L30 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND CPC:(A61K31/19*) | 05-May-2015 | 3 |
| L29 | CPC:(C07D251/18*) | 05-May-2015 | 2299 |
| L28 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND CPC:(C07D251/18*) | 05-May-2015 | 1 |
| L27 | IC:(C07D251/18*) | 05-May-2015 | 4152 |
| L26 | TAC:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND IC:(C07D251/18*) | 05-May-2015 | 12 |
| L25 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND IC:(C07D251*) | 05-May-2015 | 1 |

| | | | |
|---|---|---|---|
| L24 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND IC:(C07D*) | 05-May-2015 | 17 |
| L23 | IC:(A61K31/19*) | 05-May-2015 | 171388 |
| L22 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND IC:(A61K31/19*) | 05-May-2015 | 1 |
| L21 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND IC:(A61K31*) | 05-May-2015 | 35 |
| L20 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND IC:(A61K*) | 05-May-2015 | 52 |
| L19 | TA:((cancer* OR tumor*)) AND TACD:((polymer* wp solvent* wp (water* w2 soluble) wp dispersion*)) | 05-May-2015 | 426 |
| L18 | TA:((cancer* OR tumor*)) AND TACD:((polymer* wp solvent* wp water* wp dispersion*)) AND ASNN:(agios) | 05-May-2015 | 7 |
| L17 | TA:((cancer* OR tumor*)) AND TACD:((polymer* wp solvent* wp water* wp dispersion*)) | 05-May-2015 | 1869 |
| L16 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND TACD:(polymer* wp solvent* wp water*) | 05-May-2015 | 1 |
| L15 | TA:((cancer* OR tumor*) AND ("idh1" OR "idh2")) AND TACD:(polymer* wp solvent* wp water* wp solubl*) | 05-May-2015 | 0 |
| L14 | TA:((cancer* OR tumor*)) AND TACD:(crystalline AND (water wp solvent*)) AND TAC:("idh1" OR "idh2") | 05-May-2015 | 8 |
| L13 | TA:((cancer* OR tumor*)) AND TACD:(crystalline AND amorphous* AND (water wp solvent*)) AND TAC:("idh1" OR "idh2") | 05-May-2015 | 1 |
| L12 | TA:((cancer* OR tumor*)) AND TACD:(crystalline AND amorphous* AND (weight wp percent* wp crystal*)) AND TAC:("idh1" OR "idh2" OR glioma OR cholangiocarcin* OR chondrosarcoma* OR prostate* OR colon OR melanoma) | 05-May-2015 | 133 |
| L11 | TA:((cancer* OR tumor*)) AND TACD:(crystalline AND amorphous* AND (weight wp percent* wp crystal*)) AND TAC:("idh1" OR "idh2") | 05-May-2015 | 1 |
| L10 | TA:((cancer* OR tumor*)) AND TACD:(crystalline AND amorphous* AND (weight wp percent* wp crystal*)) | 05-May-2015 | 334 |
| L9 | TA:((cancer* OR tumor*)) AND TACD:(crystalline AND amorphous* AND (weight wp percent*)) | 05-May-2015 | 3586 |
| L8 | TAC:("idh1" AND (cancer* OR tumor*)) AND TACD:(crystalline AND amorphous*) | 05-May-2015 | 1 |
| L7 | TAC:(("idh1" AND (cancer* OR tumor*)) AND (crystalline AND amorphous*)) | 05-May-2015 | 0 |
| L6 | TAC:(crystal* AND "idh1") | 05-May-2015 | 12 |
| L5 | TAC:(crystal* AND amorph*) AND ASNN:(agios) | 05-May-2015 | 0 |
| L4 | TAC:(crystal*) AND ASNN:(AGIOS) | 04-May-2015 | 3 |
| L3 | TAC:(tumor*) AND ASNN:(AGIOS) | 04-May-2015 | 18 |
| L2 | TA:(tumor*) AND ASNN:(AGIOS) | 04-May-2015 | 0 |
| L1 | ASNN:(AGIOS) | 04-May-2015 | 268 |

**Patent Database Search Strategy/Results:**

**Non-Patent Literature (NPL) Search Strategy/Results:**

**Google Scholar:**

**05 May 2015:**

| | |
|---|---|
| cancer tumor allele IDH1 | 3700 |
| cancer tumor allele IDH1 chondrosarcoma | 224 |
| cancer tumor allele IDH1 glioma | 2300 |
| cancer tumor allele IDH1 glioma cellulose polymer | 51 |
| cancer tumor allele IDH1 glioma cellulose polymer MRI | 17 |

**ProQuest:**

**05 May 2015:**

| | |
|---|---|
| allele AND IDH1 | 123 |
| allele AND IDH1 AND cellulose | 1 |
| allele AND IDH1 AND polymer | 0 |

**EBSCO:**

**05 May 2015:**

| | |
|---|---|
| allele AND IDH1 | 5581 |
| allele AND IDH1 AND cellulose | 542 |
| allele AND IDH1 AND cellulose AND polymer | 206 |

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE



**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | 1797 |
| Examiner Name | C. Hixson |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | | | | | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 20100273808 | A1 | 2010-10-28 | Armitage et al. | |
| | 2 | 20110086088 | A1 | 2011-04-14 | Berry | |
| | 3 | 20120121515 | A1 | 2012-05-17 | Dang et al. | |
| | 4 | 20120129865 | A1 | 2012-05-24 | WANG et al. | |
| | 5 | 20120238576 | A1 | 2012-09-20 | Tao et al. | |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 6 | 20130109643 | A1 | 2013-05-02 | Riggins et al. | |
| | 7 | 20130184222 | A1 | 2013-07-18 | Popovici-Muller et al. | |
| | 8 | 20130190249 | A1 | 2013-07-25 | Lemieux et al. | |
| | 9 | 20140187435 | A1 | 2014-07-03 | Dang et al. | |
| | 10 | 20150018328 | A1 | 2015-01-15 | Konteatis et al. | |
| | 11 | 20150031627 | A1 | 2015-01-29 | Lemieux et al. | |
| | 12 | 20150044716 | A1 | 2015-02-12 | Balss et al. | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2014015422 | WO | A1 | 2014-01-30 | Ontario Inst For Cancer Res | | |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|
| | 1 | International Preliminary Report on Patentability for International Application No. PCT/CN2012/000841 dated September 10, 2012 | |
| | 2 | International Preliminary Report on Patentability for International Application No. PCT/CN2012/077096 dated September 17, 2012 | |
| | 3 | International Search Report and Written Opinion for Internatinal Application No. PCT/US2013/064601 dated February 24, 2014 | |
| | 4 | International Search Report and Written Opinion for International Application No. PCT/US15/020349 dated June 15, 2015 | |
| | 5 | International Search Report and Written Opinion for International Application No. PCT/US2015/020346 dated June 18, 2015 | |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | 1797 |
| | Examiner Name | C. Hixson |
| | Attorney Docket Number | C2081-701320 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| Signature | /Asimina T. Georges Evangelinos/ | Date (YYYY-MM-DD) | 2016-02-11 |
|---|---|---|---|
| Name/Print | Asimina T. Georges Evangelinos | Registration Number | 66888 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: February 11, 2016
Electronic Signature for Asimina T. Georges Evangelinos: /Asimina T. Georges Evangelinos/

Docket No.: C2081-701320
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Leonard Luan C Dang et al.

Application No.: 13/939,519 Confirmation No.: 2110

Filed: July 11, 2013 Art Unit: 1797

For: METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS Examiner: C. Hixson

**INFORMATION DISCLOSURE STATEMENT (IDS)**

Commissioner for Patents

Dear Sir:

Pursuant to 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed more than three months after the U.S. filing date, OR more than three months after the date of entry of the national stage of a PCT application, AND after the mailing date of the first Office Action on the merits, whichever occurs first, but before the mailing date of any of a Final Office Action, a Notice of Allowance (37 C.F.R. § 1.97(c)) or an action that otherwise closes prosecution in the application.

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

Applicant would like to bring to the Examiner's attention the following co-pending U.S. applications that may contain subject matter related to this application:

| Publication No. | Filing Date | Docket (C2081) |
|---|---|---|
| US-2013-0197106-A1 | 31-Mar-2011 | 7028US |
| US-2013-0184222-A1 | 15-Jul-2011 | 7031US |
| US-2013-0183281-A1 | 20-Apr-2012 | 703320 |
| US-2013-0035329-A1 | 08-Jun-2012 | 702220 |
| US-2014-0206673-A1 | 18-Jun-2012 | 7047US |
| US-2014-0213580-A1 | 18-Jun-2012 | 7048US |
| US-2015-0087600-A1 | 21-Jan-2013 | 7052US |
| US-2015-0299115-A1 | 11-Oct-2013 | 7054US |
| US-2015-0018328-A1 | 11-Jul-2014 | 706010 |
| US-2015-0240286-A1 | 02-Oct-2014 | 703322 |

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. § 1.56(a) exists. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98 and the Examiner is respectfully requested to consider the listed references.

Please charge our Deposit Account No. 50/2762 in the amount of $180.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 50/2762, under Order No. C2081-701320.

Dated: February 11, 2016

Respectfully submitted,
By: /Asimina T. Georges Evangelinos/
Asimina T. Georges Evangelinos
Registration No.: 66,888
LANDO & ANASTASI LLP
One Main Street, Suite 1100
Cambridge, Massachusetts 02142
(617) 395-7000
Attorney/Agent for Applicant

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 13939519 |
| **Filing Date:** | 11-Jul-2013 |
| **Title of Invention:** | METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS |
| **First Named Inventor/Applicant Name:** | Leonard Luan C. Dang |
| **Filer:** | Asimini T. Georges Evangelinos/Kelly Burke |
| **Attorney Docket Number:** | C2081-701320 |

Filed as Large Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Extension - 2 months with $0 paid | 1252 | 1 | 600 | 600 |
| **Miscellaneous:** | | | | |
| Submission- Information Disclosure Stmt | 1806 | 1 | 180 | 180 |
| | | **Total in USD ($)** | | **780** |

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 24890662 |
| **Application Number:** | 13939519 |
| **International Application Number:** | |
| **Confirmation Number:** | 2110 |
| **Title of Invention:** | METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS |
| **First Named Inventor/Applicant Name:** | Leonard Luan C. Dang |
| **Customer Number:** | 94970 |
| **Filer:** | Asimini T. Georges Evangelinos |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | C2081-701320 |
| **Receipt Date:** | 11-FEB-2016 |
| **Filing Date:** | 11-JUL-2013 |
| **Time Stamp:** | 16:32:19 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $780 |
| RAM confirmation Number | 3145 |
| Deposit Account | 502762 |
| Authorized User | GEORGES EVANGELINOS, ASIMINA T. |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees)<br>Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees) | |

Charge any Additional Fees required under 37 CFR 1.19 (Document supply fees)

Charge any Additional Fees required under 37 CFR 1.20 (Post Issuance fees)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Amendment/Req. Reconsideration-After Non-Final Reject | Amendment_in_Response_to_Non-Final_Office_Action_Under_37_CFR__1.pdf | 47691<br>757090804dcffbe45d1969a1da2cbcf93d254a7c | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Extension of Time | Two_Month_Request_for_Extension_of_Time_Under_37_CFR_1.pdf | 23854<br>e44a0469326baba0366129d06998bd2b45583ef7 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Non Patent Literature | C2081-7048WO_IPRP.pdf | 870703<br>a76268adcc96a20e9458b8d7b038b98067981e51 | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Non Patent Literature | C2081-7047WO_IPRP.pdf | 972303<br>aa792375ac7d6f71685fade363361d7f9a35187a | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Non Patent Literature | C2081-7054WO_International_Search_Report.pdf | 2292069<br>687e7a8150c73c7a96557481734c242228a43a4c | no | 16 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Non Patent Literature | C2081_7070WO_ISR_Final.pdf | 2249669<br>61107bc1dc9f8b8d139473c23ef93acd9e385a6f | no | 13 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 7 | Non Patent Literature | C2081_7069WO_ISR_Final.pdf | 2248671<br>87d276d9a3578aec019d75876bde4bb8a5d41fb8 | no | 13 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 8 | Information Disclosure Statement (IDS) Form (SB08) | Information_Disclosure_Statement_Fillable_PDF.pdf | 1035808<br>d66d3f5a88439bd75350f857c7681297319477de | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 9 | Transmittal Letter | Information_Disclosure_Statement.pdf | 25450<br>d998c912e973b9c0831f8f034fe348804fcd32bd | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 10 | Foreign Reference | WO2014015422A1.pdf | 5183497<br>3dab64adb11fd50840147d1248c5464ee3ce45c0 | no | 92 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 11 | Fee Worksheet (SB06) | fee-info.pdf | 32829<br>2d2345b66820cb2858e2e5895482562846 55d2bc | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | | **Total Files Size (in bytes):** | 14982544 | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


| PATENT APPLICATION FEE DETERMINATION RECORD<br>Substitute for Form PTO-875 | Application or Docket Number<br>13/939,519 | Filing Date<br>07/11/2013 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY**: ☒ LARGE ☐ SMALL ☐ MICRO

## APPLICATION AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | RATE ($) | FEE ($) |
|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | |
| ☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | |

## APPLICATION AS AMENDED – PART II

| AMENDMENT | 02/11/2016 | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|
| | Total (37 CFR 1.16(i)) | * 15 | Minus | ** 20 | = 0 | X $80 = | 0 |
| | Independent (37 CFR 1.16(h)) | * 1 | Minus | ***3 | = 0 | X $420 = | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | |
| | | | | | | TOTAL ADD'L FEE | **0** |

| AMENDMENT | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|
| | Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | |
| | | | | | | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/YOLANDA A. MIDDLETON/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 13/939,519 | 07/11/2013 | Leonard Luan C. Dang | C2081-701320 | 2110 |

94970 7590 09/11/2015

LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

| EXAMINER | |
|---|---|
| HIXSON, CHRISTOPHER | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1797 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 09/11/2015 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DOCKETING@LALaw.COM
GENGELSON@LALaw.COM

| Office Action Summary | Application No. 13/939,519 | Applicant(s) DANG ET AL. | |
|---|---|---|---|
| | Examiner Christopher A. Hixson | Art Unit 1797 | AIA (First Inventor to File) Status No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *7/31/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5)☒ Claim(s) *41-99* is/are pending in the application.

5a) Of the above claim(s) *57-62 and 66-79* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *41-56,63-65 and 80-99* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *7/31/2015,3/12/2014,3/12/2014*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

1. The present application is being examined under the pre-AIA first to invent provisions.

## DETAILED ACTION

2. The election of Group I, claims 46-56, 90-92, and 96-99, without traverse in the applicant's reply dated 31 July 2015 is acknowledged. The examiner withdraws the previously required election of species. Claims 41-99 are pending. Claims 57-62 and 66-79 stand withdrawn. Claims 41-45, 63-65, 80-89, and 93-95 were previously identified as linking claims generic to all groups. Therefore, claims 41-56, 63-65, 80-89, and 90-99 are considered on the merits below.

### *Priority*

3. The examiner believes that the earliest possible support for the claims can be traced to US 61/173,518, filed 28 April 2009. No support for the correlation between mutants of IDH1 and IDH2 and 2HG neoactivity, required by all claims as filed, can be found in earlier priority documents.

***Claim Interpretation/Rejections - 35 USC § 112***

4. The examiner notes that the word "neoactivity" is defined by the applicant's specification. Provisional application 61/160,253 is incorporated by reference into the present disclosure in [0001]. On p.3 of the '253 application, neoactivity is said to mean an activity which arises as a result of a mutation of an enzyme. In [0018] of the present specification, 2HG neoactivity is defined to "refer[] to the ability to convert alpha ketoglutarate to 2-hydroxyglutarate (sometimes referred to herein as 2HG)" because of the mutation of an enzyme.

5. The examiner notes that in claim 41, one is required to "select [the] subject as having an IDH1 or IDH2 allele having 2HG neoactivity." The applicants appear to define "select" to mean "selecting in whole or part on said basis," in [0624]. While the definition appears to be circular (to select means selecting), it still seems clear, because selecting is the act of making a choice based (here, at least partly) on a given preference or criterion. As such, the examiner understands that a selection is the mental or computational act of choosing based on pre-specified programming or rules. Therefore, the limitation at issue seems to require the practitioner of the method to have knowledge that any particular IDH1 and/or IDH2 allele in the subject selected has (or lacks) 2HG neoactivity. In other words, that the alleles encode (or at least that the evidence provided in the other steps of the method requires that such alleles are necessarily present which encode) for 2HG neoactivity is the rule for determining whether the IDH1 and/or IDH2 alleles found in the subject are to be selected. Even if

one selected a subject having an IDH1 and/or IDH2 allele on the basis of some other criterion and it then coincidently had 2HG neoactivity, this is would not meet the limitation of claim 41, because that is a different type of selection. Furthermore, as laid out below, the examiner believes that this correlation was first discovered by the applicants and first published in a work which is not prior art for the present application. Therefore any claim requiring knowledge of this correlation, such as claim 41 (by virtue of the limitation discussed here), will not be rejected on the basis of prior art by the examiner.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. **Claims 41-56, 63-65, and 80-99** are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

Each of these claims includes limitations described in function. For example, in claim 41, one is "the IDH1 or IDH2 neoactivity phenotype of [the] subject." Another describes an enzyme (or gene which encodes it) as having “2HG neoactivity." While these phrases imply a structural difference in the gene/enzyme being discussed, they do so in terms of a description of the change in function due to a mutational difference, rather than specify the change in structure.

Of course, functional claiming is expressly allowed. However, the courts have particularly noted a problem found in such types of claims. Namely, when one makes a claim to a genus, one must describe a sufficient number of representative species to support such a claim. The required number of such species varies on a case-by-case basis. (see MPEP 2163). Note especially that “[a] definition by function alone ‘does not suffice’ to sufficiently describe a coding sequence ‘because it is only an indication of what the gene does, rather than what it is.’” *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406. The examiner OFFICIALLY NOTES that the functional result of a mutation (or really, the correlation between any genetic sequence and its function barring close matches to known sequences) is generally unpredictable.

Specifically regarding claim 41, "analyzing a parameter related to the IDH1 or IDH2 neoactivity phenotype of said subject" requires one to analyze some otherwise unspecified thing which results from IDH1 or IDH2 neoactivity. As far as the examiner can tell, the only neoactivity discussed in the context of this invention is 2HG neoactivity. The disclosure is to a specific parameter involving a limited number of established mutations, such as discussed in [0040]-[0041]. Applicants have failed to support the entire genus of parameters encompassed by claim 41 and dependents, and these claims stand rejected on this basis.

Further regarding claim 41, in the selecting step, one is to select a subject which has an IDH1 or IDH2 allele having 2GH neoactivity. Again, only a limited number of mutations are said to correspond to this trait, such as discussed in [0040]-[0041], but applicants have laid claim to a selecting step involving all such mutations, even those unknown to them. Applicants have failed to support the entire genus of selection steps encompassed by claim 41 and dependents, and these claims stand rejected on this basis.

Regarding claim 93, steps (b)-(d) require detection of an enzyme, RNA, or DNA mutated such that it has 2HG neoactivity. Again, only a limited number of mutations are said to correspond to this trait, such as discussed in [0040]-[0041], but applicants have laid claim to steps of analyzing to determine the presence, distribution, or level of such things corresponding to all such mutations, even those unknown to them. Applicants have failed to support the entire genus of such steps encompassed by claim 93 and dependents, and these claims stand rejected on this basis.

8. **Claims 41-56, 63-65, and 80-99** are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for correlating the presence of mutated enzyme, RNA, and/or DNA with 2HG neoactivity, does not reasonably provide enablement for merely correlating the presence (in excess or not) of 2HG (or of the neoactivity of the enzyme which produces it) with 2HG neoactivity or with disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

With respect to the issue of enablement, attention is directed to the factors to be considered as laid out in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (see MPEP 2164).

***a. The breadth of the claims and the nature of the invention***

Regarding claim 41, in relevant part, the claim is to a method of evaluating a subject by analyzing a sample from a subject for the presence of 2HG (which the claims imply also essentially corresponds to evidence of neoactivity of the recited enzymes) and then based on this analysis "selecting said subject as having an IDH1 or IDH2 allele having 2HG neoactivity" (where this method lies within the scope of the claim, and dependents, particularly claims 42 and 43).

Regarding claim 93, one is to evaluate a subject for cancer (or cancer susceptibility) based on (at least) the result of an analysis the presence, distribution, or level of 2HG in a subject who does not have 2-HG aciduria.

In each of these claims, practically the only manipulative step required is a test for 2GH, the rest being mental or computational steps. As such, the claims are construed quite broadly, even in the more limited scope at issue here.

***b. The state of the prior art***

The examiner notes that the prior art indicates the elevated 2HG can occur in conditions unrelated to that which the present invention concerns itself. For example, the Genetics Home Reference Website L2HGDH entry teaches that 2HG can become elevated in a different disorder unrelated to IDH (namely, an error in L-2-hydroxyglutarate dehydrogenase allows excess 2HG to accumulate). So the examiner concludes that elevated 2HG does not necessarily correlate with IDH 2HG neoactivity. Therefore, when the analyzing step includes simply determining the presence or level of 2HG or even when it includes determining the "presence of 2HG neoactivity" (which the examiner believes is essentially the same thing), the examiner does not know how this can be distinguished between the correlation the applicant recites or some other known (or even unknown) correlation.

***c. The level of one of ordinary skill***

The skill is at the postgraduate level.

***d. The level of predictability in the art***

The examiner OFFICIALLY NOTES that molecular biology is a generally unpredictable field.

***e. The amount of direction provided by the inventor and the existence of working examples***

The examiner sees no guidance or working examples demonstrating enablement provided by the application on the issue he raises here.

***f. The quantity of experimentation needed***

Based on the analysis above, the examiner deems that an undue amount of experimentation would be required to practice the invention, as no guidance is provided to surmount the issue either in the art or by the applicant's disclosure.

## *Claim Rejections - 35 USC § 101*

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

**Claims 41-56, 63-65, 80-99** are rejected under 35 U.S.C. 101 because the claimed invention is directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more.

Claim(s) 41 is/are directed to both a method which includes both a natural law and an abstract idea. The natural law is the correlation between the elevated presence of 2HG because of the 2HG neoactivity of mutant IDH1 and/or IDH2 enzymes. The abstract idea is the selection step.

The claim(s) does/do not include additional elements that are sufficient to amount to significantly more than the judicial exception because the only manipulative step is to

measure for the presence of a certain element of the recited correlation. The analysis step is recited quite generically, and because it is a necessary step to gather information for the abstract idea and is otherwise necessary to make much use of the natural correlation, it cannot be said to add anything significantly more to the claim.

Dependent claims fail to add anything significantly more, and many simply raise new issues of subject matter eligibility. For example claims 84-92 explicitly recite business method steps which are plainly abstract and would separately allow for rejection of the claims because nothing exists in their parent claims to be significantly more than the abstract idea they recite.

Claims such as claim 47-49 (and 97-98) for example recite particulars of the analysis step, but LC-MS is simply an overwhelmingly conventional technique for biochemical analysis. The examiner OFFICIALLY NOTES that MRI has been used to detect particular molecules in a subject (see the molecular MRI field), but see especially Sosnovik et al. (Curr Op Biotech 2007), pp.7-8, and it is considered also conventional by the examiner. The examiner does not see that these limitations add something significantly more as is required.

Claim(s) 93 is/are directed to the correlation of the result of one of the steps recited in (a)-(d) with cancer or the susceptibility for cancer in a subject, which is a natural law and/or an abstract idea (the correlation is a natural law, the implied diagnosis is an abstract idea). The claim(s) does/do not include additional elements that are sufficient to amount to significantly more than the judicial exception because, as above, the claims recite only generically the necessary steps at a level so high that the

examiner simply sees this as the instruction to "apply" the recited natural law.

Dependent claims fail for the reasons also outlined above.

***Discussion of Prior Art***

10. Above, the examiner indicated his conclusion that the correlation between IDH1 and/or IDH2 mutation and 2HG neoactivity was first discovered by the applicants and first published in a work which is not prior art for the present application. As evidence for his conclusion, the examiner refers to the following references. First, Lou (Nature 2009) writes in an article that this correlation was first published in a paper written by the applicants (p.1, the Agios study), after the priority date established by the examiner, see Dang et al. (Nature 2009). Secondly, Aghili et al. (J. Neurooncology 2009), in a work published a few months before the priority date indicates that the metabolic pathway and enzymatic defect in a disease which was characterized by elevated 2HG (and is otherwise similar in nature to what is described by the applicants in their disclosure) was not well known (p.233). Given this evidence, and no other evidence demonstrating that this correlation was known before the priority date, the examiner finds no prior art rejection possible for claim 41 which requires knowledge of this correlation.

***Claim Rejections - 35 USC § 102***

11. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. **Claims 93-99** are rejected under pre-AIA 35 U.S.C. 102(a) as being anticipated by Aghili et al. (J. Neurooncology 2009, but published Oct 2008).

Regarding claims 93, 96, and 99, Aghili teaches that he evaluated a subject for the presence of susceptibility to a cancer (Table 1, correlating cancer with urinary 2-HG) by analyzing a sample from the subject for the presence and level of 2HG (Table 1). The subject does not have and is not diagnosed with 2-HG aciduria (p.234, final 2 lines – p.235, first 4 lines, where not all patients evaluated have 2-HG aciduria).

Regarding claims 94 and 95, the cancer is an astrocytic tumor and a glioblastoma (p.235 and Fig. 2, gilal tissue).

Regarding claims 97 and 98, the analysis is done with MRI (p.235, severe underlying white matter signal abnormailites characteristic of L-2-OHGA).

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least

one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more

information about eTerminal Disclaimers, refer to

http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

14. **Claims 41-99** are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 8,883,438. Although the claims at issue are not identical, they are not patentably distinct from each other because of the rationale provided below.

As one example, an analysis involving claim 93 will be presented. Other grounds exist for other claims. A side by side comparison with claim 93 with claim 1 of the '438 patent is presented here.

| | |
|---|---|
| A method of evaluating a subject for the presence or susceptibility to a cancer comprising analyzing the subject or a sample from the subject for one or more of: | A method of diagnosing a subject having a cell proliferation-related disorder or suspected of having a cell proliferation-related disorder characterized by: |
| the presence, distribution, or level of a mutant IDH1 enzyme or mutant IDH2 enzyme, either of which has 2HG neoactivity; | the presence, distribution, or level of an isocitrate dehydrogenase 1 enzyme having a mutation at residue 97 wherein the glycine residue has been replaced with an aspartic acid residue (IDH1-G97D), which has 2-hydroxyglutarate (2HG) neoactivity, wherein 2HG neoactivity is the ability to convert alpha ketoglutarate to 2-hydroxyglutarate, |
| thereby evaluating the subject for such cancer. | thereby diagnosing the subject for the cell proliferation-related disorder. |

15. **Claims 41-99** are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 7 of copending Application No. 14/504,983 (reference application). Although the claims at issue are not identical, they are not

patentably distinct from each other because claim 7 is very similar to claim 1 of the '438 patent recited above.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher A. Hixson whose telephone number is (571)270-5027. The examiner can normally be reached on M-F 9 am - 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lyle Alexander can be reached on (571)272-1254. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christopher A. Hixson/
Primary Examiner, Art Unit 1797

| Notice of References Cited | Application/Control No. 13/939,519 | Applicant(s)/Patent Under Reexamination DANG ET AL. | |
|---|---|---|---|
| | Examiner Christopher A. Hixson | Art Unit 1797 | Page 1 of 2 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | CPC Classification | US Classification |
|---|---|---|---|---|---|---|
| | A | US- | | | | |
| | B | US- | | | | |
| | C | US- | | | | |
| | D | US- | | | | |
| | E | US- | | | | |
| | F | US- | | | | |
| | G | US- | | | | |
| | H | US- | | | | |
| | I | US- | | | | |
| | J | US- | | | | |
| | K | US- | | | | |
| | L | US- | | | | |
| | M | US- | | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | CPC Classification |
|---|---|---|---|---|---|---|
| | N | | | | | |
| | O | | | | | |
| | P | | | | | |
| | Q | | | | | |
| | R | | | | | |
| | S | | | | | |
| | T | | | | | |

**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | Aghili, Mahdi et al. "Hydroxyglutaric aciduria and malignant brain tumor: a case report and literature review." J. Neurooncol. (2009) 91 233-236. |
| | V | Dang, Lenny et al. "Cancer-associated IDH1 mutations produce 2-hydroxyglutarate." Nature (2009) 462 739-746. |
| | W | Lou, Kai-Jye. "IDH1: function follows form." SciBX 2009 1-2. |
| | X | Sosnovik, David E. et al. "Emerging concepts in molcular MRI." Curr. Op. Biotech. (2007) 18 4-10. |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

| Notice of References Cited | Application/Control No. 13/939,519 | Applicant(s)/Patent Under Reexamination DANG ET AL. | |
|---|---|---|---|
| | Examiner Christopher A. Hixson | Art Unit 1797 | Page 2 of 2 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | CPC Classification | US Classification |
|---|---|---|---|---|---|---|
| | A | US- | | | | |
| | B | US- | | | | |
| | C | US- | | | | |
| | D | US- | | | | |
| | E | US- | | | | |
| | F | US- | | | | |
| | G | US- | | | | |
| | H | US- | | | | |
| | I | US- | | | | |
| | J | US- | | | | |
| | K | US- | | | | |
| | L | US- | | | | |
| | M | US- | | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | Classification |
|---|---|---|---|---|---|---|
| | N | | | | | |
| | O | | | | | |
| | P | | | | | |
| | Q | | | | | |
| | R | | | | | |
| | S | | | | | |
| | T | | | | | |

**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | Genetics Home Reference. "L2HGDH." accessed by the examiner at <http://ghr.nlm.nih.gov/gene/L2HGDH> on 4 September 2015. |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 3755322 | | 1973-08-28 | Winter et al. | |
| | 2 | 3867383 | | 1975-02-18 | Winter | |
| | 3 | 8133900 | | 2012-03-13 | Hood et al. | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 20090163508 | A1 | 2009-06-25 | KORI et al. | |
| | 2 | 20100129350 | A1 | 2010-05-27 | Zacharie et al. | |
| | 3 | 20120202818 | A1 | 2012-08-09 | Tao et al. | |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 4 | 20120277233 | A1 | 2012-11-01 | Tao et al. | | |
| | 5 | 20130190287 | A1 | 2013-07-25 | Cianchetta et al. | | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2004050033 | WO | A2 | 2004-06-17 | Arqule, Inc, | | ☐ |
| | 2 | 2005060956 | WO | A1 | 2005-07-07 | University Of Maryland, Baltimore, | | ☐ |
| | 3 | 2009016410 | WO | A2 | 2009-02-05 | Astrazeneca Ab | | ☐ |
| | 4 | 2010144404 | WO | A1 | 2010-12-16 | Abraxis Bioscience, Llc | | ☐ |
| | 5 | 2012160034 | WO | A1 | 2012-11-29 | Bayer Intellectual Property Gmbh, | | ☐ |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 1 | CAIRNS et al. "Oncogenic Isocitrate Dehydrogenase Mutations: Mechanisms, Models, and Clinical Opportunities" Cancer Discovery (2013) Vol 3, Iss 7, pp 730-741 | ☐ |
| | 2 | Cecil Text Book of Medicine, edited by BENNET and PLUM, (1997) 20th edition, Volume 1, pp 1004-1010 | ☐ |
| | 3 | DAVIS et al. "Biochemical, Cellular, and Biophysical Characterization of a Potent Inhibitor of Mutant Isocitrate Dehydrogenase IDH1" The Journal of Biological Chemistry (2014) vol 289, No 20, pp 13717-13725 | ☐ |
| | 4 | DERMER "another Anniversary for the War on Cancer" Bio/Technology (1994) Vol 12, p 320 | ☐ |
| | 5 | FRESHNEY et al. "Culture of Animal Cells, A Manual of Basic Techniques" Alan R. Liss, Inc. (1983) pp 1-6 | ☐ |
| | 6 | GOLUB et al. "Molecular Classification of Cancer: Class Discovery and Class Prediction by Gene Expression Monitoring" Science (1999) Vol 286, pp 531-537 | ☐ |
| | 7 | International Search Report and Written Opinion for International Application No. PCT/US2014/049469 dated January 22, 2015 | ☐ |
| | 8 | KRELL et al., "IDH mutations in tumorigenesis and their potential role as novel therapeutic targets" Future Oncology (2013) Vol 9, Iss 12, pp 1923-1935 | ☐ |
| | 9 | KUSAKABE et al. Chemical Abstracts vol. 152, No. 191956, Abstract for WO2010007756 (2010) | ☐ |
| | 10 | LIU et al. "Inhibition of Cancer-Associated Mutant Isocitrate Dehydrogenases: Synthesis, Structure - Activity Relationship, and Selective Antitumor Activity" Journal of Medicinal Chemistry (2014) vol 57, pp 8307-8318 | ☐ |
| | 11 | PARONIKYAN et al. "Synthesis and biological activity of 3-piperazinylpyrano [3,4-C] pyridines" Armyanskii Khimicheskii Zhurnal (1990) Vol. 43, No. 8, pp 518-523 | ☐ |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 12 | The radiation fact sheet published by the National Cancer Institute, http://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/radiation-fact-sheet, reviewed June 30, 2010 | ☐ |
| | 13 | ZHENG et al. "Synthesis and antitumor evaluation of a novel series of triaminotriazine derivatives" Bioorganic & Medicinal Chemistry (2007) Vol 15, pp 1815-1827 | ☐ |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| | | | |
|---|---|---|---|
| Examiner Signature | /Christopher Adam Hixson/ | Date Considered | 09/04/2015 |

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Catherine M. McCarty/ | Date (YYYY-MM-DD) | 2015-07-31 |
| Name/Print | Catherine M. McCarty | Registration Number | 54301 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

**EAST Search History**

**EAST Search History (Prior Art)**

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| S1 | 1 | 13/939519.app. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/03 15:14 |
| S2 | 5995 | (isocitrat$4 with dehydrogenas$4) OR IDH OR IDH1 OR IDH2 OR IDH-1 OR IDH-2 | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:04 |
| S4 | 2563 | 2HG OR ("2"?hydroxyglut$6) or (hydroxyglut$6) OR "2"?HG | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:06 |
| S5 | 223 | S2 and S4 | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:09 |
| S6 | 6 | ((Leonard) near2 (Dang)).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:37 |
| S7 | 7 | ((Valeria) near2 (Fantin)).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:38 |
| S8 | 50 | ((Stefan) near2 (Gross)).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:38 |
| S9 | 685 | ((Hyun) near2 (Jang)).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:38 |
| S10 | 17 | ((Shengfang) near2 (Jin)).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:38 |
| S11 | 149 | ((Francesco) near2 (Salituro)).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:38 |
| S12 | 105 | ((Jeffrey) near2 (Saunders)).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:39 |
| S13 | 28 | ((Shin-San) near2 (Su)).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:39 |

| | | | | | | |
|---|---|---|---|---|---|---|
| S14 | 2 | ((Katharine) near2 (Yen)).INV. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:39 |
| S15 | 991 | S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:47 |
| S16 | 16 | S2 and S15 | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:47 |
| S17 | 14 | S16 and S4 | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 07:47 |
| S18 | 1 | "8883438".did. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 08:09 |
| S19 | 1 | "20120121515".did. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 08:13 |
| S20 | 24 | neoactiv$4 | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 08:17 |
| S21 | 8612348 | C12Q1/32.cpc. "20130101" CPOI C12Q1/6886 "20130101" CPOI A61B5/055 "20130101" CPOI G06F19/328 "20130101" CPC-CURRENT: TYPE CPC DATE CPCI C12Y101/01042 "20130101" CPCI G06F19/328 "20130101" CPCI G01N33/574 "20130101" CPCI C12Q1/6886 "20130101" CPCI A61B5/055 "20130101" CPCI C12Q1/32 "20130101" CPCI A61K31/41 "20130101" CPCI A61K31/426 "20130101" CPCI A61K45/06 "20130101" CPCI C12N15/1137 "20130101" CPCI A61K31/41 "20130101" CPCI A61K31/426 "20130101" CPCA C12N2310/14 "20130101" CPCA A61K2300/00 "20130101" CPCA A61K2300/00 "20130101" | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 09:08 |
| S22 | 8612348 | C12Q1/32.cpc. C12Q1/6886 "20130101" CPOI A61B5/055 "20130101" CPOI G06F19/328 "20130101" CPC-CURRENT: TYPE CPC DATE CPCI C12Y101/01042 "20130101" CPCI G06F19/328 "20130101" CPCI G01N33/574 "20130101" CPCI C12Q1/6886 "20130101" CPCI A61B5/055 "20130101" CPCI C12Q1/32 "20130101" CPCI A61K31/41 "20130101" CPCI A61K31/426 "20130101" CPCI A61K45/06 "20130101" CPCI C12N15/1137 "20130101" CPCI A61K31/41 "20130101" CPCI A61K31/426 "20130101" CPCA C12N2310/14 "20130101" CPCA A61K2300/00 "20130101" CPCA A61K2300/00 "20130101" | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 09:08 |

| | | | | | | |
|---|---|---|---|---|---|---|
| S23 | 106810 | C12Q1/32.cpc. or C12Q1/6886.cpc. or A61B5/055.cpc. or G06F19/328.cpc. or C12Y101/01042.cpc. or G06F19/328.cpc. or G01N33/574.cpc. or C12Q1/6886.cpc. or A61B5/055.cpc. or C12Q1/32.cpc. or A61K31/41.cpc. or A61K31/426.cpc. or A61K45/06.cpc. or C12N15/1137.cpc. or A61K31/41.cpc. or A61K31/426.cpc. or C12N2310/14.cpc. or A61K2300/00.cpc. or A61K2300/00.cpc. | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 09:11 |
| S24 | 564 | S2 and S23 | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 09:11 |
| S25 | 34 | S4 and S24 | US-PGPUB; USPAT; USOCR | OR | OFF | 2015/09/04 09:11 |

**9/4/2015 2:12:17 PM**
**C:\Users\chixson\Documents\EAST\Workspaces\13939519.wsp**

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 5834485 | | 1998-11-10 | Dyke et al. | |
| | 2 | 5965559 | | 1999-10-12 | Faull et al. | |
| | 3 | 5984882 | | 1999-11-16 | Rosenschein et al. | |
| | 4 | 6313127 | | 2001-11-06 | Waterson et al. | |
| | 5 | 6399358 | | 2002-06-04 | Williams et al. | |
| | 6 | 6723730 | | 2004-04-20 | Bakthavatchalam et al. | |
| | 7 | 6979675 | | 2005-12-27 | Tidmarsh | |
| | 8 | 7173025 | | 2007-02-06 | Stocker et al. | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

Receipt date: 03/12/2014

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 20030095958 | | 2003-05-22 | Bhisetti et al. | |
| | 2 | 20030109527 | | 2003-06-12 | Jin et al. | |
| | 3 | 20030207882 | A1 | 2003-11-06 | Stocker et al. | |
| | 4 | 20040067234 | | 2004-04-08 | Einat et al. | |
| | 5 | 20040248221 | | 2004-12-09 | Stockwell | |
| | 6 | 20060281122 | | 2006-12-14 | Bryant et al. | |
| | 7 | 20080300208 | | 2008-12-04 | Einat et al. | |
| | 8 | 20090093526 | | 2009-04-09 | Miller et al. | |
| | 9 | 20100331307 | | 2010-12-30 | Salituro et al. | |

EFS Web 2.1.17 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

Receipt date: 03/12/2014

| | | | | | | |
|---|---|---|---|---|---|---|
| | 10 | 20120121515 | | 2012-05-17 | Dang et al. | |
| | 11 | 20120164143 | | 2012-06-28 | TEELING et al. | |
| | 12 | 20130035329 | | 2013-02-07 | Saunders et al. | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | 0384228 | EP | A1 | 1990-08-29 | Dainippon Pharmaceutical Co., Ltd | | ☐ |
| | 2 | 0385237 | EP | A2 | 1990-09-05 | Dainippon Pharmaceutical Co., Ltd | | ☐ |
| | 3 | 11158073 | JP | | 1999-06-15 | Takeda Chemical Industries LTD | | ☒ |
| | 4 | 2001016097 | WO | A1 | 2001-03-08 | Sugen, Inc | | ☐ |
| | 5 | 2004/073619 | WO | A2 | 2004-09-02 | Smithkline Beecham Corp | | ☐ |
| | 6 | 2004/074438 | WO | A2 | 2004-09-02 | Smithkline Beecham Corp | | ☐ |

EFS Web 2.1.17 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

Receipt date: 03/12/2014

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 7 | 2006-038594 | WO | A1 | 2006-04-13 | Ono Pharmaceutical Co et al. | | ☐ |
| | 8 | 2006070198 | WO | A1 | 2006-07-06 | Astex Therapeutics Ltd | | ☐ |
| | 9 | 2007023186 | WO | A1 | 2007-03-01 | Applied Research Systems et al. | | ☐ |
| | 10 | 2008/050168 | WO | A1 | 2008-05-02 | Ritcher Gedeon Nyrt et al. | | ☐ |
| | 11 | 2008131547 | WO | A1 | 2008-11-06 | Prometic Biosciences Inc | | ☐ |
| | 12 | 2009013126 | WO | A1 | 2009-01-29 | Nerviano Medical Sciences Srl | | ☐ |
| | 13 | 2009150248 | WO | A1 | 2009-12-17 | Cytomics Systems | | ☐ |
| | 14 | 2010/028099 | WO | A1 | 2010-03-11 | Univ Johns Hopkins | | ☐ |
| | 15 | 2010007756 | WO | A1 | 2010-01-21 | Shionogi & Co., Ltd | | ☒ |
| | 16 | 2010105243 | WO | A1 | 2010-09-16 | Agios Pharmaceuticals, Inc | | ☐ |
| | 17 | 2010144338 | WO | A1 | 2010-12-16 | Abraxis Bioscience, Llc | | ☐ |

EFS Web 2.1.17 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

Receipt date: 03/12/2014

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 18 | 2011/072174 | WO | A1 | 2011-06-16 | Agios Pharmaceuticals, Inc | | ☐ |
| | 19 | 2011002817 | WO | A1 | 2011-01-06 | Agios Pharmaceuticals, Inc | | ☐ |
| | 20 | 201105210 | WO | A1 | 2011-01-13 | Milux Holding Sa [lu] | | ☐ |
| | 21 | 2012/009678 | WO | A1 | 2012-01-19 | Agios Pharmaceuticals, Inc | | ☐ |
| | 22 | 2012/009678 | WO | A1 | 2012-01-19 | Agios Pharmaceuticals, Inc | | ☐ |
| | 23 | 2735127 | FR | A1 | 1996-12-13 | Pf Medicament | | ☐ |
| | 24 | 4099768 | JP | | 1992-03-31 | Dainippon Seiyaku | | ☒ |
| | 25 | 9291034 | JP | A | 1997-11-11 | Yoshitomi Pharmaceuticals Industries, Ltd. | | ☒ |
| | 26 | 97/28129 | WO | A1 | 1997-08-07 | Zeneca Ltd et al. | | ☐ |

If you wish to add additional Foreign Patent Document citation information please click the Add button **Add**

**NON-PATENT LITERATURE DOCUMENTS** **Remove**

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|

EFS Web 2.1.17 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

Receipt date: 03/12/2014

| | | | |
|---|---|---|---|
| | 1 | AGHILI et al. "Hydroxyglutaric aciduria and malignant brain tumor: a case report and literature review", Journal of Neuroncology, 2008. 91:233-236 | ☐ |
| | 2 | BALSS, "Analysis of the IDH1 codon 132 mutation in brain tumors", Acata Neuropathol (2008) volume 116, pages 597-602. | ☐ |
| | 3 | BENNER et al, "Evolution, language and analogy in functional genomics", Trends in Genetics (2001) volume 17, pages 414-418. | ☐ |
| | 4 | BLEEKER et al., "IDH1 mutations at residue p.R132 (IDH1 (R132)) occur frequently in high-grade 18-22 gliomas but not in other solid tumors." Hum Muta1., January 2009, Vol 30, No 1, pp 7-11; | ☐ |
| | 5 | COCCO et al. "Synthesis of Triflouromethylated Pyridinecarbonitriles" Journal of Heterocyclic Chemistry, 1995. Volume 32 pp 543-545 | ☐ |
| | 6 | DANG et al., "Cancer-associated IDH1 mutations produce 2-hydroxyglutarate." Nature, 10 29-32 December 2009, Vol 462, No 7274, pp 739-744. | ☐ |
| | 7 | Dang, Lenny, " Cancer-associated IDH1 mutations produce 2-hydroxyglutarate", Nature, Vol:462,Nr:7274,Page(s):739 - 744, 2009. | ☐ |
| | 8 | EP Search Report & Written Opinion for EP 10825706 Dated 03/20/13 | ☐ |
| | 9 | European Search Report for Application No. 10751525.6 dated 12/14/2012 | ☐ |
| | 10 | Eurpoean Search Report for EP Application No. 11763425.3 dated September 23, 2013 | ☐ |
| | 11 | HARTMANN et al. "Type and Frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1010 diffuse gliomas" Acta Neuropathologica (2009) 118: 469-474 | ☐ |

EFS Web 2.1.17 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 Receipt date: 03/12/2014 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 12 | HOLMES et al, 750 MHz 1H NMR spectroscopy characterisation of the complex metabolic pattern of urine from patients with inborn errors of metabolism: 2-hydroxyglutaric aciduria and maple syrup urine disease., Journal of Pharmaceutical and Biomedical Analysis (1997) volume 15, pages 1647-1659 | ☐ |
| | 13 | International Preliminary Report for related application No. PCT/US2010/059778 dated June 12, 2012 | ☐ |
| | 14 | International Preliminary Report on Patentability for PCT/CN2012/000841 dated December 17, 2013 | ☐ |
| | 15 | International Preliminary Report on Patentability for PCT/CN2012/077096 dated December 17, 2013 | ☐ |
| | 16 | International Preliminary Report on Patentability for PCT/US2010/027253 mailed 09/13/11. | ☐ |
| | 17 | International Preliminary Report on Patentability for PCT/US2010/040486 dated 1/12/12 | ☐ |
| | 18 | International Preliminary Report on Patentability for PCT/US2010/053623 dated April 24, 2012 | ☐ |
| | 19 | International Preliminary Report on Patentability for PCT/US2010/053624 dated 4/7/2011 | ☐ |
| | 20 | International Preliminary Report on Patentability for PCT/US2011/030692 dated October 2, 2012 | ☐ |
| | 21 | International Preliminary Report on Patentability for PCT/US2011/067752 dated April 11, 2013 | ☐ |
| | 22 | International Search Report & Written Opinion for PCT/CN2013/070755 dated April 25, 2013 | ☐ |

 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 Receipt date: 03/12/2014 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 23 | International Search Report for PCT/2011/030692 dated 7/27/2011 | ☐ |
| | 24 | International Search Report for PCT/CN2012/000841 dated September 27, 2012 | ☐ |
| | 25 | International Search Report for PCT/CN2012/077096 dated 10/4/2012 | ☐ |
| | 26 | International Search Report for PCT/CN2013/000009 dated April 18, 2013 | ☐ |
| | 27 | International Search Report for PCT/CN2013/000068 dated 04/25/13. | ☐ |
| | 28 | International Search Report for PCT/US10/040486 dated September 1, 2010. | ☐ |
| | 29 | International Search Report for PCT/US2010/027253 mailed 08/19/10. | ☐ |
| | 30 | International Search Report for PCT/US2010/059778 dated 03/17/11. | ☐ |
| | 31 | International Search Report for PCT/US2010/53623 dated January 18, 2011 | ☐ |
| | 32 | International Search Report for PCT/US2010053624 dated 4/7/2011 | ☐ |
| | 33 | International Search Report for PCT/US2011/067752 dated February 22, 2012 | ☐ |

EFS Web 2.1.17 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

Receipt date: 03/12/2014

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 34 | International Search Report for PCT/US2011044254 dated 5/10/2011 | ☐ |
| | 35 | International Search Report for PCT/US2013/064601 dated February 24, 2014 | ☐ |
| | 36 | JENNINGS et al, Expression and mutagenesis of mammalian cytosolic NADP+-specific isocitrate dehydrogenase, Biochemistry (1997)volume 36, pages 13743-13747 | ☐ |
| | 37 | KIM et al " Ser95, Asn97, and Thr78 are important for the catalytic function of porcine NADP-dependent isocitrate dehydrogenase" Protein Science (2005) 14: pp140-147 | ☐ |
| | 38 | KIM et al. "Identification and Functional Characterization of a Novel, Tissue-specific NAD1-dependent Isocitrate Dehydrogenase b Subunit Isoform" JBC. 24 December 1999, Vol 274 No. 52 pages 36866-36875 | ☐ |
| | 39 | Kranendijk, Martijn, "IDH2 Mutations in Patients with D-2-Hydroxyglutaric Aciduria" Sciences, Vol:330,Page(s):336, 2010. | ☐ |
| | 40 | MAY et al, How many species are there on earth, Science (1988) volume 241, page 1441 | ☐ |
| | 41 | PARSONS et al. "An Integrated Genomic Analysis of Human Glioblastoma Multiforme" Science Vol 321 (2008) pp 1807-1812 and Supplemental Data | ☐ |
| | 42 | POLLARD et al, "Cancer. Puzzling patterns of predisposition." Science. 10 April 2009, Vol 324, 1-5,15-16, 18-22,35-38 No 5924, pp 192-194. | ☐ |
| | 43 | POPOVICI-MULLER, Janeta et al. Discovery of the First Potent Inhibitors of Mutant IDH1 That Lower Tumor2-HG in Vivo. ACS Medicinal Chemistry Letters. 17 Sep. 2012 (17. 09. 2012), vol. 3, no. 10, 850-855 | ☐ |
| | 44 | PUBCHEM CID 4078245 [online]; September 13, 2005 [retrieved on February 4, 2012]; retrieved from http://pubchem.ncbi.nim.nih.gov/; 2d-structure | ☐ |

EFS Web 2.1.17 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

Receipt date: 03/12/2014

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 45 | PUBCHEM CID 4854170 [online]; September 17, 2005 [retrieved on February 4, 2012]; retrieved from http://pubchem.ncbi.nim.nih.gov/; 2d-structure | ☐ |
| | 46 | REITMAN et al. "Isocitrate Sehydrogenase 1 and 2 Mutations in Cancer: Alterations at a Crossroads of Cellular Metabolism" Journal of the National Cancer Institute, Vol. 102, No. 13, pp 932-941 (2010). | ☐ |
| | 47 | ROHLE et al. "An Inhibitor of Mutant IDH1 Delays Growth and Promotes Differentiation of Glioma Cells" Science, Vol. 340, No. 6132 pp 626-630 (2013) | ☐ |
| | 48 | SIRKANYAN, S.N. et al "Synthesis of new derivatives of piperazine-substituted pyrano[3,4-c]pyridines. Hayastani Kimiakan Handes 2009, Vol. 62, No 3-4 pp 378-385. English Abstract Only. | ☐ |
| | 49 | Sonoda, Yukihiko, " Analysis of IDH1 and IDH2 mutations in Japanese glioma patients" Cancer Science, Vol:100,Nr:10,Page(s):1996 - 1998, 2009. | ☐ |
| | 50 | STN File CA, Registry Number 1023444-33-8, entered STN on May 29, 2008, Chemical Abstracts Index Name "Benzenesulfonamide, 3-[[4-(1,3-benzodioxol-5-ylmethyl)-1-piperazinyl]carbonyl]-N-(4-butylphenyl)-4-methyl-" | ☐ |

If you wish to add additional non-patent literature document citation information please click the Add button **Add**

**EXAMINER SIGNATURE**

| | | | |
|---|---|---|---|
| Examiner Signature | /Christopher Adam Hixson/ | Date Considered | 09/04/2015 |

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

Receipt date: 03/12/2014

## CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

## SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Asimina T. Georges Evangelinos/ | Date (YYYY-MM-DD) | 2014-03-12 |
| Name/Print | Asimina T. Georges Evangelinos | Registration Number | 66888 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

# BIB DATA SHEET

**CONFIRMATION NO. 2110**

| SERIAL NUMBER | FILING or 371(c) DATE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 13/939,519 | 07/11/2013<br>RULE | 436 | 1797 | C2081-701320 |

**APPLICANTS**

**INVENTORS**

Leonard Luan C. Dang, Boston, MA;
Valeria Fantin, La Jolla, CA;
Stefan Gross, Brookline, MA;
Hyun Gyung Jang, Arlington, MA;
Shengfang Jin, Newton, MA;
Francesco Gerald Salituro, Marlborough, MA;
Jeffrey Owen Saunders, Lincoln, MA;
Shin-San Michael Su, Newton, MA;
Katharine Yen, Wellesley, MA;

**** CONTINUING DATA ***************************

This application is a CON of 13/256,396 11/29/2011 ABN
which is a 371 of PCT/US2010/027253 03/12/2010
which claims benefit of 61/160,253 03/13/2009
and claims benefit of 61/160,664 03/16/2009
and claims benefit of 61/173,518 04/28/2009
and claims benefit of 61/180,609 05/22/2009
and claims benefit of 61/220,543 06/25/2009
and claims benefit of 61/227,649 07/22/2009
and claims benefit of 61/229,689 07/29/2009
and claims benefit of 61/253,820 10/21/2009
and claims benefit of 61/266,929 12/04/2009

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

08/09/2013

| Foreign Priority claimed ☐ Yes ☑ No<br>35 USC 119(a-d) conditions met ☐ Yes ☐ No<br>Verified and Acknowledged /CHRISTOPHER HIXSON/ Examiner's Signature | ☐ Met after Allowance<br>Initials | STATE OR COUNTRY | SHEETS DRAWINGS | TOTAL CLAIMS | INDEPENDENT CLAIMS |
|---|---|---|---|---|---|
| | | MA | 49 | 59 | 2 |

**ADDRESS**

LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142
UNITED STATES

**TITLE**

METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS

| | | |
|---|---|---|
| | | ☐ All Fees |

BIB (Rev. 05/07).

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | | | | | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | | | | | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | | | | | | | ☐ |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

Receipt date: 03/12/2014

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 1 | STN File CA, Registry Number 1090629-29-0, entered STN on December 28, 2008, Chemical Abstracts Index Name "Benzenesulfonamide, 3-[[4-[(2,5-dimethoxyphenyl)methyl]-1-piperazinyl]carbonyl]-N-(4-methoxyphenyl)-4-methyl-" | ☐ |
| | 2 | STN File CA, Registry Number 134538-28-6, entered STN on June 28, 1991, Chemical Abstracts Index Name "1H-Pyrano[3,4-c]pyridine-5-carbonitrile, 3,4-dihydro-3,3-dimethyl-6-[4-(1-oxobutyl)-1-piperazinyl]-8-phenyl-", disclosed in Paronikyan et al. Armyanskii Khimicheskii Zhurnal, 1990, Vol 43, No.8 | ☐ |
| | 3 | STN File CA, Registry Number 134538-29-7, entered STN on June 28, 1991, Chemical Abstracts Index Name "1H-Pyrano[3,4-c]pyridine-5-carbonitrile, 3,4-dihydro-3,3-dimethyl-6-[4-(2-methyl-1-oxopropyl)-1-piperazinyl]-8-phenyl-", disclosed in Paronikyan et al. Armyanskii Khimicheskii Zhurnal, 1990, Vol 43, No.8 | ☐ |
| | 4 | STN File CA, Registry Number 134538-30-0, entered STN on June 28, 1991, Chemical Abstracts Index Name "1H-Pyrano[3,4-c]pyridine-5-carbonitrile, 6-(4-benzoyl-1-piperazinyl)-3,4-dihydro-3,3-dimethyl-8-phenyl-", disclosed in Paronikyan et al. Armyanskii Khimicheskii Zhurnal, 1990, Vol 43, No.8 | ☐ |
| | 5 | STN File CA, Registry Number 134538-31-1, entered STN on June 28, 1991, Chemical Abstracts Index Name "1H-Pyrano[3,4-c]pyridine-5-carbonitrile, 6-[4-(2-furanylcarbonyl)-1-piperazinyl]-3,4-dihydro-3,3-dimethyl-8-phenyl-", disclosed in Paronikyan et al. Armyanskii Khimicheskii Zhurnal, 1990, Vol 43, No.8 | ☐ |
| | 6 | STN File CA, Registry Number 713505-78-3, entered STN on July 21, 2004, Chemical Abstracts Index Name "1-Piperazinecarboxylic acid, 4-[4-methyl-3-[(phenylamino)sulfonyl]benzoyl]-, ethyl ester" | ☐ |
| | 7 | STN File CA, Registry Number 847757-57-7, entered STN on April 1, 2005, Chemical Abstracts Index Name "Benzenesulfonamide, 3-[[4-(1,3-benzodioxol-5-ylmethyl)-1-piperazinyl]carbonyl]-N-(4-ethoxyphenyl)-N,4-dimethyl-" or "Piperazine, 1-(1,3-benzodioxol-5-ylmethyl)-4-[5-[[(4-ethoxyphenyl)methylamino]sulfonyl]-2-methylbenzoyl]-" | ☐ |
| | 8 | STN REGISTRY, L23 ANSWER 2 OF 3 (CAS NUMBER: 1032450-21-7), Database: ASINEX Ltd.,Entered STN: 03 Jul2008 (03. 07. 2008) | ☐ |
| | 9 | STNREGISTRY. L23 ANSWER 1 OF 3 (CAS NUMBER: 1038821-72-5),Database: ChemDB (University of California Irvine), Entered STN: 05 Aug. 2008 (05. 08. 2008) | ☐ |
| | 10 | STRUYS et al, Investigations by mass isotopomer analysis of the formation of D-2-hydroxyglutarate by cultured lymphoblasts from two patients with D-2-hydroxyglutaric aciduria, FEBS letters 92004 volume 557, pages 115-120 | ☐ |
| | 11 | STRUYS et al. "Mutations in the D-2-hydroxyglutarate dehydrogenase gene cause D-2-hydroxyglutaric aciduria" American Journal of Human Genetics, 2005. 76:358-360 | ☐ |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

Receipt date: 03/12/2014

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 12 | Supplementary European Search Report for EP Application No. 10825707.2 dated June 28, 2013 | ☐ |
| | 13 | Supplementary Search Report for EP10794668 Mailed 10/18/12. | ☐ |
| | 14 | Supplimentary European Search Report for EP 10751525 Mailed December 14, 2012. | ☐ |
| | 15 | THOMPSON, "Metabolic Enzymes as Oncogenes or Tumor Suppressors." The New England 18-22 Journal of Medicine, 19 February 2009, Vol 360, No 8, pp 813-815; pg 813, pg 815, col 1; Fig 1. | ☐ |
| | 16 | WANG et al. "A novel ligand N,N?-di(2-pyridyl)-2,4-diamino-6-phenyl-1,3,5-triazine (dpdapt) and its complexes: [Cu (dpdapt)Cl2] and [Cu(dpdapt)(NO3)(H2O)] · NO3 · H2O" Polyhedron, 2006. Vol 25, Issue 1. pp 195-202 | ☐ |
| | 17 | Ward, Patrick S, "The Common Feature of Leukemia-Associated IDH1 and IDH2 Mutations Is a Neomorphic Enzyme Activity Converting [alpha]-Ketoglutarate to 2-Hydroxyglutarate" Cancer cell, Vol:17,Nr:3,Page(s):225 - 234, 2010. | ☐ |
| | 18 | WATANABE et al., "IDH1 Mutations Are Early Events in the Development of Astrocytomas and Oligodendrogliomas". American Journal of Pathology, April 2009 (published online 26 February (2009), Vol 174, No 4, pp 1149-1153; Abstract, pg 1150, col 1. | ☐ |
| | 19 | Written Opinion for PCT/US2010/027253 mailed 08/19/10. | ☐ |
| | 20 | Written Opinion of International Search Authority for PCT/CN2013/000009 dated April 18, 2013 | ☐ |
| | 21 | Written Opinion of Search Authority for PCT/US2010/53623 dated January 18, 2011 | ☐ |
| | 22 | Written Opinion of the International Searching Authority for PCT/US2011/067752 dated March 5, 2012 | ☐ |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

Receipt date: 03/12/2014

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 23 | YAN et al., "IDH1 and IDH2 Mutations in Gliomas." The New England Journal of Medicine, 19 18-22 February 2009, Vol 360, No. 8, pp 765-73. | ☐ |
| | 24 | ZHAO ET AL: "Glioma-derived mutations in IDH1 dominantly inhibit IDH1 catalytic activity and induce HIF-1alpha", SCIENCE, vol. 324, no. 5924, 10 April2009 (2009-04-10), pages 261-265 | ☐ |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | /Christopher Adam Hixson/ | Date Considered | 09/04/2015 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

Receipt date: 03/12/2014

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|---|---|---|---|
| Signature | /Asimina T. Georges Evangelinos/ | Date (YYYY-MM-DD) | 2014-03-12 |
| Name/Print | Asimina T. Georges Evangelinos | Registration Number | 66888 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

~~ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CAH/~~

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | Examiner | Art Unit |
| | CHRISTOPHER A HIXSON | 1797 |

| CPC- SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| A61B5/055 | 4 sept 2015 | cah |
| A61K31/41,426 | 4 sept 2015 | cah |
| A61K45/06 | 4 sept 2015 | cah |
| A61K2300/00 | 4 sept 2015 | cah |
| C12N15/1137 | 4 sept 2015 | cah |
| C12N2310/14 | 4 sept 2015 | cah |
| C12Q1/32,6886 | 4 sept 2015 | cah |
| C12Y101/01042 | 4 sept 2015 | cach |
| G01N33/574 | 4 sept 2015 | cah |
| G06F19/328 | 4 sept 2015 | cah |

| CPC COMBINATION SETS - SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| US CLASSIFICATION SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

| SEARCH NOTES | | |
|---|---|---|
| Search Notes | Date | Examiner |
| searched in east as attached, inventor name search, google.com, scholar.google.com | 4 sept 2015 | cah |

| INTERFERENCE SEARCH | | | |
|---|---|---|---|
| US Class/ CPC Symbol | US Subclass / CPC Group | Date | Examiner |
| | | | |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | **Examiner** | **Art Unit** |
| | CHRISTOPHER A HIXSON | 1797 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/04/2015 | | | | | | | | |
| | 1 | - | | | | | | | | |
| | 2 | - | | | | | | | | |
| | 3 | - | | | | | | | | |
| | 4 | - | | | | | | | | |
| | 5 | - | | | | | | | | |
| | 6 | - | | | | | | | | |
| | 7 | - | | | | | | | | |
| | 8 | - | | | | | | | | |
| | 9 | - | | | | | | | | |
| | 10 | - | | | | | | | | |
| | 11 | - | | | | | | | | |
| | 12 | - | | | | | | | | |
| | 13 | - | | | | | | | | |
| | 14 | - | | | | | | | | |
| | 15 | - | | | | | | | | |
| | 16 | - | | | | | | | | |
| | 17 | - | | | | | | | | |
| | 18 | - | | | | | | | | |
| | 19 | - | | | | | | | | |
| | 20 | - | | | | | | | | |
| | 21 | - | | | | | | | | |
| | 22 | - | | | | | | | | |
| | 23 | - | | | | | | | | |
| | 24 | - | | | | | | | | |
| | 25 | - | | | | | | | | |
| | 26 | - | | | | | | | | |
| | 27 | - | | | | | | | | |
| | 28 | - | | | | | | | | |
| | 29 | - | | | | | | | | |
| | 30 | - | | | | | | | | |
| | 31 | - | | | | | | | | |
| | 32 | - | | | | | | | | |
| | 33 | - | | | | | | | | |
| | 34 | - | | | | | | | | |
| | 35 | - | | | | | | | | |
| | 36 | - | | | | | | | | |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | **Examiner** | **Art Unit** |
| | CHRISTOPHER A HIXSON | 1797 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/04/2015 | | | | | | | | |
| | 37 | - | | | | | | | | |
| | 38 | - | | | | | | | | |
| | 39 | - | | | | | | | | |
| | 40 | - | | | | | | | | |
| | 41 | ✓ | | | | | | | | |
| | 42 | ✓ | | | | | | | | |
| | 43 | ✓ | | | | | | | | |
| | 44 | ✓ | | | | | | | | |
| | 45 | ✓ | | | | | | | | |
| | 46 | ✓ | | | | | | | | |
| | 47 | ✓ | | | | | | | | |
| | 48 | ✓ | | | | | | | | |
| | 49 | ✓ | | | | | | | | |
| | 50 | ✓ | | | | | | | | |
| | 51 | ✓ | | | | | | | | |
| | 52 | ✓ | | | | | | | | |
| | 53 | ✓ | | | | | | | | |
| | 54 | ✓ | | | | | | | | |
| | 55 | ✓ | | | | | | | | |
| | 56 | ✓ | | | | | | | | |
| | 57 | N | | | | | | | | |
| | 58 | N | | | | | | | | |
| | 59 | N | | | | | | | | |
| | 60 | N | | | | | | | | |
| | 61 | N | | | | | | | | |
| | 62 | N | | | | | | | | |
| | 63 | ✓ | | | | | | | | |
| | 64 | ✓ | | | | | | | | |
| | 65 | ✓ | | | | | | | | |
| | 66 | N | | | | | | | | |
| | 67 | N | | | | | | | | |
| | 68 | N | | | | | | | | |
| | 69 | N | | | | | | | | |
| | 70 | N | | | | | | | | |
| | 71 | N | | | | | | | | |
| | 72 | N | | | | | | | | |

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 13939519 | DANG ET AL. |
| | **Examiner** | **Art Unit** |
| | CHRISTOPHER A HIXSON | 1797 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/04/2015 | | | | | | | | |
| | 73 | N | | | | | | | | |
| | 74 | N | | | | | | | | |
| | 75 | N | | | | | | | | |
| | 76 | N | | | | | | | | |
| | 77 | N | | | | | | | | |
| | 78 | N | | | | | | | | |
| | 79 | N | | | | | | | | |
| | 80 | ✓ | | | | | | | | |
| | 81 | ✓ | | | | | | | | |
| | 82 | ✓ | | | | | | | | |
| | 83 | ✓ | | | | | | | | |
| | 84 | ✓ | | | | | | | | |
| | 85 | ✓ | | | | | | | | |
| | 86 | ✓ | | | | | | | | |
| | 87 | ✓ | | | | | | | | |
| | 88 | ✓ | | | | | | | | |
| | 89 | ✓ | | | | | | | | |
| | 90 | ✓ | | | | | | | | |
| | 91 | ✓ | | | | | | | | |
| | 92 | ✓ | | | | | | | | |
| | 93 | ✓ | | | | | | | | |
| | 94 | ✓ | | | | | | | | |
| | 95 | ✓ | | | | | | | | |
| | 96 | ✓ | | | | | | | | |
| | 97 | ✓ | | | | | | | | |
| | 98 | ✓ | | | | | | | | |
| | 99 | ✓ | | | | | | | | |

Docket No.: C2081-701320
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Leonard Luan C Dang et al.

Application No.: 13/939,519 | Confirmation No.: 2110

Filed: July 11, 2013 | Art Unit: N/A

For: METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | Examiner: Not Yet Assigned

**RESPONSE TO RESTRICTION REQUIREMENT**

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

This paper is being filed in response to the Restriction Requirement issued by the U.S. Patent & Trademark Office on May 1, 2015, in connection with the above-referenced application.

An Information Disclosure Statement and a request for a 1-month extension of time, to and including August 1, 2015, are being filed with this paper.

**Remarks** begin on page **2** of this paper.

## REMARKS

Claims Election

The Office has required restriction to one of the following Groups under 35 U.S.C. §121:

Group I: Claims 46-56, 90-92 and 96-99, drawn to methods of evaluating a subject for levels of 2HG, classified in A 61 B 5/055; and

Group II: Claims 57-62, drawn to evaluating by DNA sequencing, classified in C12Q 1/6886; and

Group III: Claims 66-79, drawn to evaluating IDH 2 protein, classified in C12Y 101/01042.

In response to the Restriction Requirement mailed May 1, 2015 in the above-identified application, Applicant hereby elects, without traverse, Group I, claims 46-56, 90-92 and 96-99, drawn to methods of evaluating a subject for levels of 2HG. Claims 46-56, 90-92 and 96-99 are encompassed by Group I.

Species Election

The Office has further required election of a species. Applicant hereby elects **acute lymphoblastic leukemia (AML)** as the species of cancer. Acute lymphoblastic leukemia is disclosed, for example, at least on page 11, of the specification as originally filed. This species reads on claims 46-56, 90-92 and 96-99.

Applicant further elects **spectroscopic analysis** as the specific analysis. **Spectroscopic analysis** is disclosed, for example, at least on page 3, of the specification as originally filed. This species reads on claims 46-56, 90-92 and 96-99.

Applicant notes that the above species elections are being made for initial search purposes only. The Office is reminded to extend the search to other non-elected species should the elected species be free of prior art, in accordance with M.P.E.P. §803.02. Moreover, upon allowance of a generic claim, Applicant is entitled to consideration of claims to additional species which depend

from or otherwise require the limitations of the allowable generic claim, as provided by 37 CFR §1.141.

## CONCLUSION

Applicant submits herewith a request for a 1-month extension of time and $200 Extension Fee. No further fee is believed due. However, if this response is not considered timely filed and if a further request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. Please charge any deficiency to Deposit Account No. 50/2762, referencing Attorney Docket No. C2081-701320.

Dated: July 31, 2015

Respectfully submitted,

Electronic signature: /Catherine M. McCarty/
Catherine M. McCarty
Registration No.: 54,301
LANDO & ANASTASI LLP
Riverfront Office Park
One Main Street
Suite 1100
Cambridge, Massachusetts 02142
(617) 395-7000
Attorney for Applicant

PTO/AIA/22 (03-13)
Approved for use through 7/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


| **PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)** | Docket Number (Optional) C2081-701320 |
|---|---|
| Application Number 13/939,519 | Filed July 11, 2013 |
| For METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | |
| Art Unit N/A | Examiner Not Yet Assigned |

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | Fee | Small Entity Fee | Micro Entity Fee | |
|---|---|---|---|---|
| [x] One month (37 CFR 1.17(a)(1)) | $200 | $100 | $50 | $ 200.00 |
| [ ] Two months (37 CFR 1.17(a)(2)) | $600 | $300 | $150 | $ |
| [ ] Three months (37 CFR 1.17(a)(3)) | $1,400 | $700 | $350 | $ |
| [ ] Four months (37 CFR 1.17(a)(4)) | $2,200 | $1,100 | $550 | $ |
| [ ] Five months (37 CFR 1.17(a)(5)) | $3,000 | $1,500 | $750 | $ |

[ ] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

[ ] A check in the amount of the fee is enclosed.

[ ] Payment by credit card. Form PTO-2038 is attached.

[x] The Director has already been authorized to charge fees in this application to a Deposit Account.

[x] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50/2762 .

[x] Payment made via EFS-Web.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

[ ] applicant.

[x] attorney or agent of record. Registration number 54,301 .

[ ] attorney or agent acting under 37 CFR 1.34. Registration number _____ .

| /Catherine M. McCarty/ | July 31, 2015 |
|---|---|
| Signature | Date |
| Catherine M. McCarty | (617) 395-7087 |
| Typed or printed name | Telephone Number |

**NOTE:** This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

[ ] * Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: July 31, 2015 Electronic Signature for Catherine M. McCarty: /Catherine M. McCarty/

2561869

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: CATHERINE M. MCCARTY
LANDO & ANASTASI LLP
RIVERFRONT OFFICE PARK
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

| | |
|---|---|
| Applicant's or agent's file reference<br>C2081-7065WO2 | Date of mailing<br>*(day/month/year)* |
| International application No.<br>PCT/US 14/49469 | **FOR FURTHER ACTION** See paragraphs 1 and 4 below |
| Applicant AGIOS PHARMACEUTICALS, INC. | International filing date<br>*(day/month/year)* 01 August 2014 (01.08.2014) |

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   **Filing of amendments and statement under Article 19:**
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   **When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   **How?** Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   **For more detailed instructions**, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   - ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

| | |
|---|---|
| Name and mailing address of the ISA/<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>Telephone No. PCT OSP: 571-272-7774 |

Form PCT/ISA/220 (July 2014)

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: CATHERINE M. MCCARTY
LANDO & ANASTASI LLP
RIVERFRONT OFFICE PARK
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 22 JAN 2015 |
| Applicant's or agent's file reference: C2081-7065WO2 | **FOR FURTHER ACTION** See paragraphs 1 and 4 below |
| International application No.: PCT/US 14/49469 | International filing date *(day/month/year)*: 01 August 2014 (01.08.2014) |

Applicant AGIOS PHARMACEUTICALS, INC.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

**Filing of amendments and statement under Article 19:**
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

**When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

**How?** Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

**For more detailed instructions,** see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   - ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

| | |
|---|---|
| Name and mailing address of the ISA/<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>Telephone No. PCT OSP: 571-272-7774 |

Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference C2081-7065WO2 | FOR FURTHER ACTION | see Form PCT/ISA/220 as well as, where applicable, item 5 below. |
|---|---|---|
| International application No. PCT/US 14/49469 | International filing date *(day/month/year)* 01 August 2014 (01.08.2014) | (Earliest) Priority Date *(day/month/year)* 02 August 2013 (02.08.2013) |
| Applicant AGIOS PHARMACEUTICALS, INC. | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**

a. the figure of the **drawings** to be published with the abstract is Figure No. 1

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/49469

**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 attached 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.:
1-6 and 15-20

**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.

**Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)**

Provided are isocitrate dehydrogenase 2 (IDH2) inhibitor compounds useful for treating cancer and methods of treating cancer, comprising administering to a subject in need thereof a compound described herein. Also provided are polymorphic forms of the IDH2 inhibitor compounds characterized by X Ray powder diffraction patterns, having improved physicochemical properties that influence in vivo dissolution rate for formulation purposes.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/49469

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/5377, A61K 31/53, C07D 401/12 (2014.01)

CPC - C07D251/18, C07D413/14, A61K31/53, C07D401/12, A61K31/5377, C07D251/26

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 - A61K 31/5377, A61K 31/53, C07D 401/12 (2014.01)
CPC - C07D251/18, C07D413/14, A61K31/53, C07D401/12, A61K31/5377, C07D251/26

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/210.2, 544/209, 514/236.2, 514/245, 544/208.5

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Minesoft Patbase, Google Scholar, PubChem: Triazin*, power diffraction, X-ray, 28 angles, 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino }-1,3,5-triazin-2-yl)amino]propan-2-ol,
C1(=NC(=NC(=N1)N(CC(C)(C)O[H])[H])N([H])C2=CC(=NC=C2)C)C3=CC=CC(=N3)C

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 2010/0129350 A1 (Zacharie et al.) 27 May 2010 (27.05.2010) para [0002], [0041] | 1-6, 15-20 |
| A | US 2012/0238576 A1 (Tao et al.) 20 September 2012 (20.09.2012) para [0027], [0071], [0075], [0076], [0218] | 1-6, 15-20 |
| A | US 2013/0190287 A1 (Cianchetta et al.) 25 July 2013 (25.07.2013) para [0148], [0163], Table 1, pg 36, Compound No. 409 | 1-6, 15-20 |

☐ 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 |
|---|---|
| 06 January 2015 (06.01.2015) | 22 JAN 2015 |

| Name and mailing address of the ISA/US | Authorized officer: |
|---|---|
| Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Attachment to Box.No.III:

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 1-6 and 15-20 directed to isolated crystalline forms of compound 3, characterized by X-ray powder diffraction patterns.

Group II: Claims 7-14 directed to isolated crystalline forms of compound 1, characterized by X-ray powder diffraction patterns.

Group III: Claims 21-48 directed to methods of treating an advanced hematologic malignancy characterized by the presence of a mutant allele of IDH2, comprising administering to a subject in need thereof, a therapeutically effective amount of compound 3 or its salt form (compound 1).

The inventions listed as Group I-III 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 includes the technical feature of an isolated crystalline form of compound 3, not shared by Groups II-III.

Group II includes the technical feature of an isolated crystalline form of compound 1, not shared by Groups I and III.

Group III includes the technical feature of a method of treating an advanced hematologic malignancy characterized by the presence of a mutant allele of IDH2, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound, not shared by Groups I-II.

Common technical features:

Groups I and III share the technical feature of a compound 3.

Groups II and III share the technical feature of compound 1.

Groups I and II share the technical feature of a compound having the core structure of compound 3 [compound 1 being the methanesulfonate salt form of compound 3 - see Applicant's specification - pg 11, para 3; pg 40, para 3].

These shared technical features, however, does not provide a contribution over the prior art as being anticipated by US 2013/0190287 A1 to Cianchetta et al. [published on 25 July 2013] (hereinafter 'Cianchetta'), which discloses compound 3, namely, 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino }-1,3,5-triazin-2-yl)amino]propan-2-ol (para [0148], Table 1, pg 36, Compound No. 409).
Cianchetta further discloses compound 1, namely, 2-Methyl-1-[(4-[6- trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino} -1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (para [0148], Table 1, pg 36, Compound No. 409; para [0163], Mesylates of each compound of Table 1 are explicitly included herein).

As said compounds were known in the art at the time of the invention these cannot be considered special technical features that would otherwise unify Group I-III.

Groups I-III, thus lack unity under PCT Rule 13.2, because they do not share a same or corresponding special technical feature providing a contribution over the prior art.

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: CATHERINE M. MCCARTY
LANDO & ANASTASI LLP
RIVERFRONT OFFICE PARK
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

# PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 22 JAN 2015 |
| Applicant's or agent's file reference<br>C2081-7065WO2 | FOR FURTHER ACTION<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US 14/49469 | 01 August 2014 (01.08.2014) | 02 August 2013 (02.08.2013) |

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/5377, A61K 31/53, C07D 401/12 (2014.01)
CPC - C07D251/18, C07D413/14, A61K31/53, C07D401/12, A61K31/5377, C07D251/26

Applicant AGIOS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to th IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Fom PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

| Name and mailing address of the ISA/US | Date of completion of this opinion | Authorized officer: |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | 06 January 2015 (06.01.2015) | Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/237 (cover sheet) (July 2011)

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

a. (means)

☐ on paper

☐ in electronic form

b. (time)

☐ in the international application as filed

☐ together with the international application in electronic form

☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:

☐ paid additional fees.

☐ paid additional fees under protest and, where applicable, the protest fee.

☐ paid additional fees under protest but the applicable protest fee was not paid.

☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

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 1-6 and 15-20 directed to isolated crystalline forms of compound 3, characterized by X-ray powder diffraction patterns.

Group II: Claims 7-14 directed to isolated crystalline forms of compound 1, characterized by X-ray powder diffraction patterns.

Group III: Claims 21-48 directed to methods of treating an advanced hematologic malignancy characterized by the presence of a mutant allele of IDH2, comprising administering to a subject in need thereof, a therapeutically effective amount of compound 3 or its salt form (compound 1).

The inventions listed as Group I-III 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 includes the technical feature of an isolated crystalline form of compound 3, not shared by Groups II-III.
Group II includes the technical feature of an isolated crystalline form of compound 1, not shared by Groups I and III.
Group III includes the technical feature of a method of treating an advanced hematologic malignancy characterized by the presence of a mutant allele of IDH2, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound, not shared by Groups I-II.

Common technical features:

Groups I and III share the technical feature of a compound 3.
Groups II and III share the technical feature of compound 1.
Groups I and II share the technical feature of a compound having the core structure of compound 3 [compound 1 being the methanesulfonate salt form of compound 3 - see Applicant's specification - pg 11, para 3; pg 40, para 3].

These shared technical features, however, does not provide a contribution over the prior art as being anticipated by US 2013/0190287 A1 to Cianchetta et al. [published on 25 July 2013] (hereinafter 'Cianchetta'), which discloses compound 3, namely, 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino }-1,3,5-triazin-2-yl)amino]propan-2-ol (para [0148], Table 1, pg 36, Compound No. 409).
Cianchetta further discloses compound 1, namely, 2-Methyl-1-[(4-[6- trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (para [0148], Table 1, pg 36, Compound No. 409; para [0163], Mesylates of each compound of Table 1 are explicitly included herein).

As said compounds were known in the art at the time of the invention these cannot be considered special technical features that would otherwise unify Group I-III.

Groups I-III, thus lack unity under PCT Rule 13.2, because they do not share a same or corresponding special technical feature providing a contribution over the prior art.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

☐ all parts.

☒ the parts relating to claims Nos. 1-6 and 15-20

**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-6, 15-20 | YES |
| | Claims | NONE | NO |
| Inventive step (IS) | Claims | 1-6, 15-20 | YES |
| | Claims | NONE | NO |
| Industrial applicability (IA) | Claims | 1-6, 15-20 | YES |
| | Claims | NONE | NO |

2. Citations and explanations:

Claims 1-6, 15-20 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed subject matter, specifically an isolated crystalline form of 2-Methyl-1-[(4-[6- trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate and its X-ray power diffraction patterns.

The best prior art on record that disclose 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino }-1,3,5-triazin-2-yl)amino]propan-2-ol (compound 3) are given below:

US 2010/0129350 A1 to Zacharie et al. (hereinafter 'Zacharie'), discloses compounds of para [0041] representing three-substituted triazine analogues and para [0002] discloses a generic structure used for cancer treatment. The structures of Zacharie do not disclose the specific substituents of the compound 3. Further, Zacharie does not disclose an X-ray powder diffraction pattern for the different structural forms of the triazine compound.

US 2012/0238576 A1 to Tao et al. (hereinafter 'Tao'), discloses a substituted triazine and its crystal form in para [0027], [0071], [0075], [0076] with anticancer activity (para [0120]). The specific examples are provided in para [0218]. Both generic structure and specific examples do not disclose the side chains of compound 3. Further Tao does not disclose an X-ray powder diffraction pattern for the different structural forms of the triazine compound.

US 2013/0190287 A1 to Cianchetta et al. (hereinafter 'Cianchetta'), discloses compound 3, namely, 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino }-1,3,5-triazin-2-yl)amino]propan-2-ol (para [0148], Table 1, pg 36, Compound No. 409).
Cianchetta further discloses compound 1, namely, 2-Methyl-1-[(4-[6- trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (para [0148], Table 1, pg 36, Compound No. 409; para [0163], Mesylates of each compound of Table 1 are explicitly included herein).
Cianchetta does not disclose an isolated crystalline form of compound 3 or its salt, having X-ray powder diffraction pattern with peaks as specified in claims 1, 3, 5, 15, 17 or 15.

There is no prior art on record that discloses the claimed subject matter, specifically an isolated crystalline form of compound 3 or its salt, having the X-ray powder diffraction patterns of the independent claims 1, 3, 5, 15, 17 and 19. These claims therefore meet the criteria set out in PCT Article 33(2)-(3).

Caims 2, 4, 6, 16, 18 and 20 are dependent from claims 1, 3, 5, 15, 17 and 19 and therefore meet the criteria set out in PCT Article 33(2)-(3) for substantially the same reasons.

Claims 1-6, 15-20 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE



# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 3755322 | | 1973-08-28 | Winter et al. | |
| | 2 | 3867383 | | 1975-02-18 | Winter | |
| | 3 | 8133900 | | 2012-03-13 | Hood et al. | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 20090163508 | A1 | 2009-06-25 | KORI et al. | |
| | 2 | 20100129350 | A1 | 2010-05-27 | Zacharie et al. | |
| | 3 | 20120202818 | A1 | 2012-08-09 | Tao et al. | |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 4 | 20120277233 | A1 | 2012-11-01 | Tao et al. | |
| | 5 | 20130190287 | A1 | 2013-07-25 | Cianchetta et al. | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2004050033 | WO | A2 | 2004-06-17 | Arqule, Inc, | | ☐ |
| | 2 | 2005060956 | WO | A1 | 2005-07-07 | University Of Maryland, Baltimore, | | ☐ |
| | 3 | 2009016410 | WO | A2 | 2009-02-05 | Astrazeneca Ab | | ☐ |
| | 4 | 2010144404 | WO | A1 | 2010-12-16 | Abraxis Bioscience, Llc | | ☐ |
| | 5 | 2012160034 | WO | A1 | 2012-11-29 | Bayer Intellectual Property Gmbh, | | ☐ |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 1 | CAIRNS et al. "Oncogenic Isocitrate Dehydrogenase Mutations: Mechanisms, Models, and Clinical Opportunities" Cancer Discovery (2013) Vol 3, Iss 7, pp 730-741 | ☐ |
| | 2 | Cecil Text Book of Medicine, edited by BENNET and PLUM, (1997) 20th edition, Volume 1, pp 1004-1010 | ☐ |
| | 3 | DAVIS et al. "Biochemical, Cellular, and Biophysical Characterization of a Potent Inhibitor of Mutant Isocitrate Dehydrogenase IDH1" The Journal of Biological Chemistry (2014) vol 289, No 20, pp 13717-13725 | ☐ |
| | 4 | DERMER "another Anniversary for the War on Cancer" Bio/Technology (1994) Vol 12, p 320 | ☐ |
| | 5 | FRESHNEY et al. "Culture of Animal Cells, A Manual of Basic Techniques" Alan R. Liss, Inc. (1983) pp 1-6 | ☐ |
| | 6 | GOLUB et al. "Molecular Classification of Cancer: Class Discovery and Class Prediction by Gene Expression Monitoring" Science (1999) Vol 286, pp 531-537 | ☐ |
| | 7 | International Search Report and Written Opinion for International Application No. PCT/US2014/049469 dated January 22, 2015 | ☐ |
| | 8 | KRELL et al., "IDH mutations in tumorigenesis and their potential role as novel therapeutic targets" Future Oncology (2013) Vol 9, Iss 12, pp 1923-1935 | ☐ |
| | 9 | KUSAKABE et al. Chemical Abstracts vol. 152, No. 191956, Abstract for WO2010007756 (2010) | ☐ |
| | 10 | LIU et al. "Inhibition of Cancer-Associated Mutant Isocitrate Dehydrogenases: Synthesis, Structure - Activity Relationship, and Selective Antitumor Activity" Journal of Medicinal Chemistry (2014) vol 57, pp 8307-8318 | ☐ |
| | 11 | PARONIKYAN et al. "Synthesis and biological activity of 3-piperazinylpyrano [3,4-C] pyridines" Armyanskii Khimicheskii Zhurnal (1990) Vol. 43, No. 8, pp 518-523 | ☐ |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 12 | The radiation fact sheet published by the National Cancer Institute, http://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/radiation-fact-sheet, reviewed June 30, 2010 | ☐ |
| | 13 | ZHENG et al. "Synthesis and antitumor evaluation of a novel series of triaminotriazine derivatives" Bioorganic & Medicinal Chemistry (2007) Vol 15, pp 1815-1827 | ☐ |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| Signature | /Catherine M. McCarty/ | Date (YYYY-MM-DD) | 2015-07-31 |
|---|---|---|---|
| Name/Print | Catherine M. McCarty | Registration Number | 54301 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: July 31, 2015
Electronic Signature for Catherine M. McCarty: /Catherine M. McCarty/

Docket No.: C2081-701320
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Leonard Luan C Dang et al.

Application No.: 13/939,519 | Confirmation No.: 2110

Filed: July 11, 2013 | Art Unit: N/A

For: METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | Examiner: Not Yet Assigned

## INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents

Dear Madam:

Pursuant to 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a first Office Action on the merits as far as is known to the undersigned (37 C.F.R. § 1.97(b)(3)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

Applicant would like to bring to the Examiner's attention the following pending U.S. applications that may contain subject matter related to this application:

| Application No. | Filing Date | Docket (C2081) |
|---|---|---|
| 14/435674 | 11-Oct-2013 | 7054US |
| 14/504983 | 02-Oct-2014 | 703322 |

| Publication No. | Filing Date | Docket (C2081) |
|---|---|---|
| US-2013-0197106-A1 | 31-Mar-2011 | 7028US |
| US-2013-0184222-A1 | 15-Jul-2011 | 7031US |
| US-2013-0190249-A1 | 18-Jan-2013 | 705110 |
| US-2015-0087600-A1 | 21-Jan-2013 | 7052US |
| US-2013-0183281-A1 | 18-Jul-2013 | 703320 |
| US-2013-0035329-A1 | 08-Jun-2012 | 702220 |
| US-2014-0206673-A1 | 18-Jun-2012 | 7047US |
| US-2014-0213580-A1 | 18-Jun-2012 | 7048US |
| US-2013-0190287-A1 | 07-Jan-2013 | 705010 |
| US-2015-0018328-A1 | 11-Jul-2014 | 706010 |
| US-2015-0031627-A1 | 25-Jul-2014 | 706410 |

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. § 1.56(a) exists. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98 and the Examiner is respectfully requested to consider the listed references.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 50/2762, under Order No. C2081-701320.

Dated: July 31, 2015

Respectfully submitted,

Electronic signature: /Catherine M. McCarty/
Catherine M. McCarty
Registration No.: 54,301
LANDO & ANASTASI LLP
One Main Street, Suite 1100
Cambridge, Massachusetts 02142
(617) 395-7000
Attorney for Applicant

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 13939519 |
| **Filing Date:** | 11-Jul-2013 |
| **Title of Invention:** | METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS |
| **First Named Inventor/Applicant Name:** | Leonard Luan C. Dang |
| **Filer:** | Catherine M. McCarty/Kelly Burke |
| **Attorney Docket Number:** | C2081-701320 |

Filed as Large Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Extension - 1 month with $0 paid | 1251 | 1 | 200 | 200 |
| **Miscellaneous:** | | | | |
| | | | **Total in USD ($)** | **200** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 23088897 |
| **Application Number:** | 13939519 |
| **International Application Number:** | |
| **Confirmation Number:** | 2110 |
| **Title of Invention:** | METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS |
| **First Named Inventor/Applicant Name:** | Leonard Luan C. Dang |
| **Customer Number:** | 94970 |
| **Filer:** | Catherine M. McCarty |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | C2081-701320 |
| **Receipt Date:** | 31-JUL-2015 |
| **Filing Date:** | 11-JUL-2013 |
| **Time Stamp:** | 20:02:04 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $200 |
| RAM confirmation Number | 6272 |
| Deposit Account | 502762 |
| Authorized User | MCCARTY, CATHERINE |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)<br>Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees) | |

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Response to Election / Restriction Filed | Response_to_Restriction_Requirement_without_Traverse.pdf | 22999<br>0c9048d18c537355ab34ea003125b02062d6a891 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Extension of Time | One_Month_Request_for_Extension_of_Time_Under_37_CFR_1.pdf | 24001<br>54f841a770cc79469223979cb609f09f1794d845 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Non Patent Literature | CAIRNS.pdf | 1775095<br>c639c7325f0bdd424c980dfb4ee286c1b416aae0 | no | 13 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Non Patent Literature | cecil_text.pdf | 1863209<br>b3a03b9feb44a1514ca21c926cca38a5b6e9ad01 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Non Patent Literature | Davis.pdf | 1060484<br>c0de22bd40b19bb43551f27b2d8e32e365748772 | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Non Patent Literature | Dermer.pdf | 165753<br>7b063d0c11c9fc618fe5784ab171588396f461bf | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 7 | Non Patent Literature | fresheny.pdf | 695436<br>137a80a845945f80721fd52d552e448a05acd7fb | no | 7 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 8 | Non Patent Literature | GOLUB.pdf | 1143054<br>250c0b63f5c3f85fefcee4395c6a9c59f7978f32 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 9 | Non Patent Literature | C2081-7065WO2_International_Search_Report.pdf | 1086576<br>241112dfd526c686060c968ddda97fb42826fb85 | no | 11 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 10 | Non Patent Literature | KRELL.pdf | 1519703<br>10c18496e6527fa67ce68e2561ecbd00aabae39e | no | 13 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 11 | Non Patent Literature | Kusakabi_et_al.pdf | 314927<br>7dcbe4dad12f8c06a9a61d18bababb8dce6cac9d7 | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 12 | Non Patent Literature | LIU.pdf | 1248776<br>c40b120ea1fb980f7ee5bde5b076399f995273fd | no | 12 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 13 | Non Patent Literature | Paronikyan.pdf | 2179480<br>56b7bef308df8c1da05965a419ec872d14c68279 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 14 | Non Patent Literature | Radiation_fact_sheet.pdf | 702388<br>d7eaa41e27d2c8ebd54d461470acc36a84207e05 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 15 | Non Patent Literature | Zhengetal.pdf | 220565<br>a73b0a96853bcf3a50528d4a916dbc499fec09f3 | no | 13 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 16 | Information Disclosure Statement (IDS) Form (SB08) | Information_Disclosure_Statement_Fillable_PDF.pdf | 613893<br>39466dfb065d74184f609191e41b158e573826e0 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 17 | Transmittal Letter | Information_Disclosure_Statement.pdf | 27670<br>f46b5541b5fff95b2efec03ac345ebebda9efb71 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 18 | Foreign Reference | WO2004050033A2.pdf | 1773294<br>661139d0bbd9c3ff67c938554a591d7d60da0d7c | no | 40 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 19 | Foreign Reference | WO2005060956A1.pdf | 4899685<br>441362cd121aa20f8d30fa2e58fbb0696e62f818 | no | 213 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 20 | Foreign Reference | WO2009016410A2.pdf | 11007500<br>0557613a9f5b3d59565e4ab9c9fbb6322d31b351 | no | 296 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 21 | Foreign Reference | WO2010144404A1.pdf | 3538945<br>9222682e9577184e43b5fdd0c0a3063486003b3b | no | 137 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 22 | Foreign Reference | WO2012160034A1.pdf | 9316486<br>766a5a28c0b9df116ca6c8a50e58f68b8380337e | no | 225 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 23 | Fee Worksheet (SB06) | fee-info.pdf | 30719<br>f2ef5a14e8f260fa419be34660166c75b51b7127 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 45230638 | | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 13/939,519 | 07/11/2013 | Leonard Luan C. Dang | C2081-701320 | 2110 |

94970 7590 05/01/2015

LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

| EXAMINER | |
|---|---|
| POHNERT, STEVEN C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 05/01/2015 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DOCKETING@LALaw.COM
GENGELSON@LALaw.COM

| Office Action Summary | Application No. 13/939,519 | Applicant(s) DANG ET AL. | |
|---|---|---|---|
| | Examiner STEVEN POHNERT | Art Unit 1634 | AIA (First Inventor to File) Status No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *7/11/2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5)☒ Claim(s) *41-99* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *41-99* are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

## DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

### *Election/Restrictions*

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 46-56,90-92, 96-99 drawn to methods of evaluating a subject for levels of 2HG, classified in A 61 B 5/055.

II. Claims 57-62, drawn to evaluating by DNA sequencing, classified in C12Q 1/6886.

III. Claims 66-79, drawn to evaluating IDH 2 protein, classified in C12Y 101/01042.

2. Claim 41-45, 63-65, 80-89, 93-95 link(s) inventions I, II and III. The restriction requirement between the linked inventions is **subject to** the nonallowance of the linking claim(s), claim 41-45, 63-65, 80-89, 93-95. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions **shall** be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104 **Claims that require all the limitations of an allowable linking claim** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, the allowable linking claim, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The inventions are distinct, each from the other because of the following reasons:

3. Inventions I and II are directed to related methods. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed methods of detecting 2HG have a materially different design and effect, do not overlap in scope and is not an obvious variant of methods of DNA sequencing. Searching both methods would place a serious search burden on the office. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

4. Inventions I and III are directed to related methods. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the

inventions as claimed methods of detecting 2HG have a materially different design and effect, do not overlap in scope and is not an obvious variant of methods of determining variants in proteins. Searching both methods would place a serious search burden on the office. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

5. Inventions II and III are directed to related methods. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed methods of detecting mutations by DNA sequencing have a materially different design and effect, do not overlap in scope and is not an obvious variant of methods of detecting variant in proteins. Searching both methods would place a serious search burden on the office. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

6. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

**Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined** even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

7. This application contains claims directed to the following patentably distinct species for election of groups I, II or III applicant must elect a specific cancer. Additionally if applicant elects group I, applicant must elect a specific analysis. If applicant elects group II or III, applicant must elect IDH1 or IDH2 and a specific mutation. The species are independent or distinct because each analysis method is distinct as it requires different reagents, conditions and apparatus. Each gene or mutation is different as it has a different nucleic acid or amino acid sequence. Each gene or mutation would require a separate search. Searching more than one analysis, mutation and gene would place a serious search burden on the office. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 41-45, 63-65, 84-93 generic.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

**Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined** even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement

will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN POHNERT whose telephone number is

(571)272-3803. The examiner can normally be reached on Monday-Friday 6:00-5:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/STEVEN POHNERT/
Primary Examiner, Art Unit 1634

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 13/939,519 | 07/11/2013 | Leonard Luan C. Dang | C2081-701320 |

**CONFIRMATION NO. 2110**

94970
LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

**PUBLICATION NOTICE**


**Title:**METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS

**Publication No.**US-2014-0187435-A1
**Publication Date:**07/03/2014

## NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

---

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 13/939,519 | 07/11/2013 | 1629 | 5660 | C2081-701320 | 59 | 2 |

**CONFIRMATION NO. 2110**

**UPDATED FILING RECEIPT**

94970
LANDO & ANASTASI, LLP
C2081
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

*OC000000067184415*

Date Mailed: 03/24/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

**Inventor(s)**

Leonard Luan C. Dang, Boston, MA;
Valeria Fantin, La Jolla, CA;
Stefan Gross, Brookline, MA;
Hyun Gyung Jang, Arlington, MA;
Shengfang Jin, Newton, MA;
Francesco Gerald Salituro, Marlborough, MA;
Jeffrey Owen Saunders, Lincoln, MA;
Shin-San Michael Su, Newton, MA;
Katharine Yen, Wellesley, MA;

**Applicant(s)**

Leonard Luan C. Dang, Boston, MA;
Valeria Fantin, La Jolla, CA;
Stefan Gross, Brookline, MA;
Hyun Gyung Jang, Arlington, MA;
Shengfang Jin, Newton, MA;
Francesco Gerald Salituro, Marlborough, MA;
Jeffrey Owen Saunders, Lincoln, MA;
Shin-San Michael Su, Newton, MA;
Katharine Yen, Wellesley, MA;

**Assignment For Published Patent Application**

AGIOS PHARMACEUTICALS, INC, Cambridge, MA

**Power of Attorney:** None

**Domestic Priority data as claimed by applicant**

This application is a CON of 13/256,396 11/29/2011 ABN

which is a 371 of PCT/US2010/027253 03/12/2010
which claims benefit of 61/160,253 03/13/2009
and claims benefit of 61/160,664 03/16/2009
and claims benefit of 61/173,518 04/28/2009
and claims benefit of 61/180,609 05/22/2009
and claims benefit of 61/220,543 06/25/2009
and claims benefit of 61/227,649 07/22/2009
and claims benefit of 61/229,689 07/29/2009
and claims benefit of 61/253,820 10/21/2009
and claims benefit of 61/266,929 12/04/2009

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

**If Required, Foreign Filing License Granted:** 08/09/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/939,519**

**Projected Publication Date:** 07/03/2014

**Non-Publication Request:** No

**Early Publication Request:** No

**Title**

METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS

**Preliminary Class**

514

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

## LICENSE FOR FOREIGN FILING UNDER

## Title 35, United States Code, Section 184

## Title 37, Code of Federal Regulations, 5.11 & 5.15

**GRANTED**

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

**NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed

from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

---

## *SelectUSA*

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

## PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/939,519

### APPLICATION AS FILED - PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY FEE($) |
|---|---|---|---|---|---|---|---|
| BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | | | N/A | 280 |
| SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | | | N/A | 600 |
| EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | | | N/A | 720 |
| TOTAL CLAIMS (37 CFR 1.16(i)) | 59 minus 20 = | * 39 | | | OR | x 80 = | 3120 |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | 2 minus 3 = | * | | | | x 420 = | 0.00 |
| APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | | | | 800 |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | | | | 0.00 |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | | | TOTAL | 5520 |

### APPLICATION AS AMENDED - PART II

AMENDMENT A

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY ADDITIONAL FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

AMENDMENT B

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE($) | ADDITIONAL FEE($) | | RATE($) | ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

Attorney Docket No.: C2081-701320
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Leonard Luan C Dang et al.

Application No.: 13/939,519 Confirmation No.: 2110

Filed: July 11, 2013 Art Unit: N/A

For: METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS Examiner: Not Yet Assigned

**RESPONSE TO NOTICE TO FILE MISSING PARTS OF APPLICATION**

Commissioner for Patents

Dear Madam:

In response to the Notice to File Missing Parts of Application mailed August 15, 2013, Applicant respectfully submits:

- $280 Basic Utility Electronic Filing Fee;
- $600 Utility Search Fee;
- $720 Utility Examination Fee;
- $800 for pages in excess of 100;
- $140 Surcharge ; and
- $3120 for Excess Claims Fees

An Information Disclosure Statement (IDS), a Declaration by the inventors filed under § 1.51(b)(2), a 5-month extension of time, and requisite fees are being filed with this paper.

Applicant respectfully requests that the corrections made in the Request for Corrected Filing Receipt filed on November 12, 2013 be reflected in the Updated Filing Receipt.

Applicant respectfully submits $8660 covering all fees believed to be due. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 50/2762, under Order No. C2081-701320.

Dated: March 12, 2014

Respectfully submitted,

By: /Asimina T. Georges Evangelinos/
Asimina T. Georges Evangelinos
Registration No.: 66,888
LANDO & ANASTASI LLP
Riverfront Office Park
One Main Street
Suite 1100
Cambridge, Massachusetts 02142
(617) 395-7000
Attorney for Applicant

| PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) | Docket Number (Optional) C2081-701320 |
|---|---|
| Application Number 13/939,519 | Filed July 11, 2013 |
| For METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | |
| Art Unit N/A | Examiner Not Yet Assigned |

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | Fee | Small Entity Fee | Micro Entity Fee | |
|---|---|---|---|---|
| ☐ One month (37 CFR 1.17(a)(1)) | $200 | $100 | $50 | $ |
| ☐ Two months (37 CFR 1.17(a)(2)) | $600 | $300 | $150 | $ |
| ☐ Three months (37 CFR 1.17(a)(3)) | $1,400 | $700 | $350 | $ |
| ☐ Four months (37 CFR 1.17(a)(4)) | $2,200 | $1,100 | $550 | $ |
| ☒ Five months (37 CFR 1.17(a)(5)) | $3000 | $1,500 | $750 | $ 3,000.00 |

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50/2762 .

☒ Payment made via EFS-Web.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

☐ applicant.

☒ attorney or agent of record. Registration Number 66,888 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____ .

/Asimina T. Georges Evangelinos/ — Signature

March 12, 2014 — Date

Asimina T. Georges Evangelinos — Typed or printed name

(617) 395-7015 — Telephone Number

**NOTE:** This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of 1 forms are submitted.

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 13939519 |
| **Filing Date:** | 11-Jul-2013 |
| **Title of Invention:** | METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS |
| **First Named Inventor/Applicant Name:** | Leonard Luan C. Dang |
| **Filer:** | Asimini T. Georges Evangelinos |
| **Attorney Docket Number:** | C2081-701320 |

Filed as Large Entity

## Utility under 35 USC 111(a) Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| Utility application filing | 1011 | 1 | 280 | 280 |
| Utility Search Fee | 1111 | 1 | 600 | 600 |
| Utility Examination Fee | 1311 | 1 | 720 | 720 |
| **Pages:** | | | | |
| Utility Appl Size fee per 50 sheets >100 | 1081 | 2 | 400 | 800 |
| **Claims:** | | | | |
| Claims in Excess of 20 | 1202 | 39 | 80 | 3120 |
| **Miscellaneous-Filing:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Late Filing Fee for Oath or Declaration | 1051 | 1 | 140 | 140 |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |
| Extension - 5 months with $0 paid | 1255 | 1 | 3000 | 3000 |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **8660** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 18446371 |
| **Application Number:** | 13939519 |
| **International Application Number:** | |
| **Confirmation Number:** | 2110 |
| **Title of Invention:** | METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS |
| **First Named Inventor/Applicant Name:** | Leonard Luan C. Dang |
| **Customer Number:** | 94970 |
| **Filer:** | Asimini T. Georges Evangelinos |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | C2081-701320 |
| **Receipt Date:** | 12-MAR-2014 |
| **Filing Date:** | 11-JUL-2013 |
| **Time Stamp:** | 16:15:13 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $8660 |
| RAM confirmation Number | 3139 |
| Deposit Account | 502762 |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)<br>Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees) | |

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Information Disclosure Statement (IDS) Form (SB08) | Information_Disclosure_Statement_Fillable_PDF_2_of_2.PDF | 614260<br>f4b186440994a87d06e31326efd677f95874f340 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems. | | | | | |
| 2 | Information Disclosure Statement (IDS) Form (SB08) | Information_Disclosure_Statement_Fillable_PDF_1_of_2.PDF | 616661<br>1873cd429c34b04eccca11e2a355d2a0e4aaeb48 | no | 12 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Transmittal Letter | Information_Disclosure_Statement.pdf | 20259<br>2ed89be9ed048e13e65ed8c3e7ecf00b0c74d49a | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Oath or Declaration filed | ORIGINAL_EXECUTED_DECLARATION_SIGNED_BY_DANG_FANTIN_GROSS_JANG_JIN_SALITURO_SAUNDERS.PDF | 436199<br>3e4e62767351bf75058e113fbbfa0e209a6802e3 | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Non Patent Literature | AGHILI_et_al.PDF | 353899<br>49ab65ec96664638e649b33508dccb188eb645d1 | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Non Patent Literature | Cocco_et_al.PDF | 142917<br>635d148a2d139e151044945c74ad6da38b1b8478 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 7 | Non Patent Literature | NPL_-_Dang_-_Cancer-associated_IDH1_mutations_produce_2-hydroxyglutarate.PDF | 2503680<br>60aa6423fede2cae2720be5c8910ea57e89293b4 | no | 18 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 8 | Non Patent Literature | 7033Ep_Search_Report.PDF | 263775<br>b8316a980539ddd3d98d0b1b8ae27c342e537e87 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 9 | Non Patent Literature | L67879PCEP_sESR__ESOP.PDF | 187944<br>cbc701272b27987eb326f76834df78ca4fb08d5e | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 10 | Non Patent Literature | ESR.PDF | 214596<br>55b5b2defacc5865ba8949d69b794508bf0c6731 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 11 | Non Patent Literature | Hartmann_et_al.PDF | 144711<br>9d86bddbfb9f2c79513070991a111641f8897962 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 12 | Non Patent Literature | C2081-7022WO_International_Preliminary_Report_on_Patentability.PDF | 584522<br>d719a6a8448ea465874780df04194613b7ed4522 | no | 11 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 13 | Non Patent Literature | IPRP_C2081-7048WO.PDF | 289367<br>aae9b4ab2380b9ae3c72243f69caf3a6e51e4805 | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 14 | Non Patent Literature | IPRP_C2081-7047WO.PDF | 324123<br>456f853495d2bf9486ef6172d91acab7caf17688 | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 15 | Non Patent Literature | C2081-7019WO_International_Preliminary_Report_on_Patentability.PDF | 266129<br>d56372fb3142d5de2774352f9964aa613fdfaecb | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 16 | Non Patent Literature | C2081-7033WO_IPRP.PDF | 282468<br>52878fdd8b5e50ea9ffbb9165be9da1be32818f1 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 17 | Non Patent Literature | C2081-7021WO_IPRP.PDF | 335268<br>a87180574b16204d70c63add74c9cb3c4f02ea31 | no | 7 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 18 | Non Patent Literature | PCTUS2011030692-ipp1-000001-EN.PDF | 475445<br>68f898b834dd4784d20c3e78df31c77bd50658ab | no | 7 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 19 | Non Patent Literature | C2081-7035Wo_preliminary_report.PDF | 560545<br>9a7d964f92051da208c81dcbc560db6e00bda873 | no | 14 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 20 | Non Patent Literature | C2081-7028WO_PCT_ISA_237_OCTOBER_11_2012.PDF | 532978<br>2b84c3577dae63bf356580acf7529c66445df726 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 21 | Non Patent Literature | C2081-7048WO_International_Search_Report.PDF | 412030<br>1e10ece4e8db649487bf5c95fdfaeff66a2ebd9c | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 22 | Non Patent Literature | C2081-7047WO.PDF | 528404<br>307ecd9eb56cbd32670a7a9b62eb6fe5f980e2d4 | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 23 | Non Patent Literature | C2081-7050WO_Search_Report.PDF | 448679<br>39097ec793c31adf1a9f96f584faa8d247268771 | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 24 | Non Patent Literature | International_Search_Report_C2081-7051WO.PDF | 394355<br>1bbae7474b320a7f9efab9e91dd248798ab9b657 | no | 13 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 25 | Non Patent Literature | C2081-7019WO_International_Search_Report_for_PCTUS1040486_dated_090110.PDF | 832837<br>109313ae7d8b5c9e2558bd85b0fb1eda13b3a555 | no | 12 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 26 | Non Patent Literature | E_F__C2081-7022WO_PCT_ISA_220_PCT_ISA_210_AND_PCT_ISA_237_MARCH_17_2011.PDF | 972730<br>03b8d2656e0e5772677a8dd2848088f9dc15fecf | no | 23 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 27 | Non Patent Literature | EF_4-28-11_C2081-7033WO_INTERNATIONAL_SEARCH_REPORT.PDF | 138179<br>ed940e47a173ee08225b87c4cce68a75e7d4360b | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 28 | Non Patent Literature | E_F__C2081-7021WO_PCT_ISA_220_APRIL_7_2011.PDF | 1581651<br>beca5909dfbe7439d05e25f8fad90b488910681e | no | 22 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 29 | Non Patent Literature | C2081-7035WO_search_report.PDF | 283651<br>eeaed15cec44bea8ada3f6691c7699d065baca0b | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 30 | Non Patent Literature | E_F__C2081-7031WO_PCT_ISA_210_PCT_ISA_220_AND_PCT_ISA_237_OCTOBER_5_2011.PDF | 7941911<br>47850547bd1a40c20d15c85a12c383d30655b956 | no | 172 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 31 | Non Patent Literature | C2081-7054WO_search_report.PDF | 608813<br>3eaa65838ecc38c0bc12dfe6d9ff69df29e31892 | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 32 | Non Patent Literature | kim_et_al.PDF | 1598522<br>e5406dc485ffb15995293b66837f5c534b5bb677 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 33 | Non Patent Literature | 1741697_1-Kim_et_al.PDF | 1170308<br>e2c09410c96b20fea3d1b2b2d0da742d42e66823 | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 34 | Non Patent Literature | NPL_-_Kranendijk_-_IDH2_Mutations_in_Patients_with_D-2-Hydroxyglutaric_Aciduria.PDF | 182819<br>11f6f66e7f726d821685d6bd999d3ddb663cc4c2 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 35 | Non Patent Literature | Parsons_et_al.PDF | 3758212<br>7cc86acd4ad99c230f49064aa1890dd87d926c61 | no | 23 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 36 | Non Patent Literature | Popovici_Muller.PDF | 892868<br>07c24ca25344969b37233221c748d0fe4244b0fe | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 37 | Non Patent Literature | Pubchem_4078245.PDF | 125668<br>1a97f197b223ebb8fa1c3438ae8f49c9698c1e6a | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 38 | Non Patent Literature | PubChem_4854170.PDF | 119693<br>070bdbf4b8cc444aabda56470c4a39d03581ecff | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 39 | Non Patent Literature | C2081-7028EP_ADVANCE_ACCESS_PUBLICATION_MAY_30_2010.PDF | 1082594<br>d8628e3680113ed958fb4c728b3c32851576d20f | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 40 | Non Patent Literature | C2081-7028EP_SCIENCEMAG_ARTICLE_SEPTEMBER_9_2013.PDF | 852853<br>acdb76bc672d7e0b8449fc9bc635a36ed8d2557e | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 41 | Non Patent Literature | chemical_journal_of_armenia.PDF | 86549<br>cb3490bc52651e1330e8b929aee12d62433b0319 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 42 | Non Patent Literature | NPL_-_Sonoda_-_Analysis_of_IDH1_and_IDH2_mutations_in_Japanese_glioma_patients.PDF | 490149<br>3f33697ae1ce54848ba86202cec498342953a065 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 43 | Non Patent Literature | 1023444-33-8.PDF | 17130<br>55b6df324cb93de7708b7a9776412 8f3d1ade6dc | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 44 | Non Patent Literature | 1090629-29-0.PDF | 17060<br>15666ba66341db0f02d768d31f1fd726dd42682c | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 45 | Non Patent Literature | 134538-28-6.PDF | 24631<br>f95e260864d00b7822ec0e55893cfc1bec5a6e51 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 46 | Non Patent Literature | 134538-29-7.PDF | 24630<br>5da3cb33f3d650ae02b9ca9325b0fc0acd2e62c1 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 47 | Non Patent Literature | 134538-30-0.PDF | 26663<br>abdc845132aa4d279f7df7ba2a8ad16ed426a3be | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 48 | Non Patent Literature | 134538-31-1.PDF | 26667<br>131912ee32bc14bc01e1acbbde1be253c991a483 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 49 | Non Patent Literature | 713505-78-3.PDF | 16860<br>34f61363078ac821ac73a3560ed253b32e08543d | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 50 | Non Patent Literature | 847757-57-7.PDF | 16857<br>c5d9cec1d28174f4233d5b2a4754e41231c79a45 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 51 | Non Patent Literature | 1032450-21-7.PDF | 14132<br>d680e16c64714f9a139971274264aac513a00a46 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 52 | Non Patent Literature | 1038821-72-5.PDF | 14612<br>e94f25f0911bd3c839b5e2325abb9c4fa326271d | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 53 | Non Patent Literature | Struys_et_al.PDF | 82435<br>7d95ee1ecb94c5d5ac3d30a16be21149f83c0f94 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 54 | Non Patent Literature | L68339PCEP_ESR.PDF | 151048<br>686c84efaec4d060ecb0003bb6ea607ae51752e7 | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 55 | Non Patent Literature | C2081-7019EP_Supplementary_Search_Report_for_EP10794668_Mailed_101812.PDF | 332557<br>3332caf50f9c2417e1dd8c9905942c2486426a1a | no | 10 |
| **Warnings:** | | | | | |
| The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing | | | | | |
| **Information:** | | | | | |
| 56 | Non Patent Literature | Wang_et_al.PDF | 667002<br>e21f911e059bee6f38117b6b798f929cc809d2ba | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 57 | Non Patent Literature | NPL_-_Ward_-_The_Common_Feature_of_Leukemia-Associated_IDH1_and_IDH2_Mutations_Is_a_Neomor.PDF | 2004901<br>abcaf7c192837b6bd594bbbd78cec2bd513b16dd | no | 23 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 58 | Non Patent Literature | 13-05-08_International_Search_Report_C2081-7050WOPPCUS13199.PDF | 474273<br>107b71db3fb0e9205f37758b52ab1b18baa7cf74 | no | 16 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 59 | Applicant Response to Pre-Exam Formalities Notice | C2081_701320_Resp_to_Missing_Parts.pdf | 20030<br>dd02c3a3470b32ec6e98594e51191f14e5bd9a5c | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 60 | Extension of Time | Extension_of_Time.pdf | 26484<br>2975e5bbb212f7c2bd25868cf3fb446bd31b4a61 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 61 | Fee Worksheet (SB06) | fee-info.pdf | 42003<br>95ebc0cd1f221ab4049d0e19ea5ff848ab6e243e | no | 2 |

| Warnings: | |
|---|---|
| Information: | |
| Total Files Size (in bytes): | 37653196 |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 18446371 |
| **Application Number:** | 13939519 |
| **International Application Number:** | |
| **Confirmation Number:** | 2110 |
| **Title of Invention:** | METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS |
| **First Named Inventor/Applicant Name:** | Leonard Luan C. Dang |
| **Customer Number:** | 94970 |
| **Filer:** | Asimini T. Georges Evangelinos |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | C2081-701320 |
| **Receipt Date:** | 12-MAR-2014 |
| **Filing Date:** | 11-JUL-2013 |
| **Time Stamp:** | 16:15:13 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $8660 |
| RAM confirmation Number | 3139 |
| Deposit Account | 502762 |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)<br>Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees) | |

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Information Disclosure Statement (IDS) Form (SB08) | Information_Disclosure_Statement_Fillable_PDF_2_of_2.PDF | 614260<br>f4b186440994a87d06e31326efd677f95874f340 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems. | | | | | |
| 2 | Information Disclosure Statement (IDS) Form (SB08) | Information_Disclosure_Statement_Fillable_PDF_1_of_2.PDF | 616661<br>1873cd429c34b04eccca11e2a355d2a0e4aaeb48 | no | 12 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Transmittal Letter | Information_Disclosure_Statement.pdf | 20259<br>2ed89be9ed048e13e65ed8c3e7ecf00b0c74d49a | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Oath or Declaration filed | ORIGINAL_EXECUTED_DECLARATION_SIGNED_BY_DANG_FANTIN_GROSS_JANG_JIN_SALITURO_SAUNDERS.PDF | 436199<br>3e4e62767351bf75058e113fbbfa0e209a6802e3 | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Non Patent Literature | AGHILI_et_al.PDF | 353899<br>49ab65ec96664638e649b33508dccb188eb645d1 | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Non Patent Literature | Cocco_et_al.PDF | 142917<br>635d148a2d139e151044945c74ad6da38b1b8478 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 7 | Non Patent Literature | NPL_-_Dang_-_Cancer-associated_IDH1_mutations_produce_2-hydroxyglutarate.PDF | 2503680<br>60aa6423fede2cae2720be5c8910ea57e89293b4 | no | 18 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 8 | Non Patent Literature | 7033Ep_Search_Report.PDF | 263775<br>b8316a980539ddd3d98d0b1b8ae27c342e537e87 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 9 | Non Patent Literature | L67879PCEP_sESR__ESOP.PDF | 187944<br>cbc701272b27987eb326f76834df78ca4fb08d5e | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 10 | Non Patent Literature | ESR.PDF | 214596<br>55b5b2defacc5865ba8949d69b794508bf0c6731 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 11 | Non Patent Literature | Hartmann_et_al.PDF | 144711<br>9d86bddbfb9f2c79513070991a111641f8897962 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 12 | Non Patent Literature | C2081-7022WO_International_Preliminary_Report_on_Patentability.PDF | 584522<br>d719a6a8448ea465874780df04194613b7ed4522 | no | 11 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 13 | Non Patent Literature | IPRP_C2081-7048WO.PDF | 289367<br>aae9b4ab2380b9ae3c72243f69caf3a6e51e4805 | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 14 | Non Patent Literature | IPRP_C2081-7047WO.PDF | 324123<br>456f853495d2bf9486ef6172d91acab7caf17688 | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 15 | Non Patent Literature | C2081-7019WO_International_Preliminary_Report_on_Patentability.PDF | 266129<br>d56372fb3142d5de2774352f9964aa613fdfaecb | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 16 | Non Patent Literature | C2081-7033WO_IPRP.PDF | 282468<br>52878fdd8b5e50ea9ffbb9165be9da1be32818f1 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 17 | Non Patent Literature | C2081-7021WO_IPRP.PDF | 335268<br>a87180574b16204d70c63add74c9cb3c4f02ea31 | no | 7 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 18 | Non Patent Literature | PCTUS2011030692-ipp1-000001-EN.PDF | 475445<br>68f898b834dd4784d20c3e78df31c77bd50658ab | no | 7 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 19 | Non Patent Literature | C2081-7035Wo_preliminary_report.PDF | 560545<br>9a7d964f92051da208c81dcbc560db6e00bda873 | no | 14 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 20 | Non Patent Literature | C2081-7028WO_PCT_ISA_237_OCTOBER_11_2012.PDF | 532978<br>2b84c3577dae63bf356580acf7529c66445df726 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 21 | Non Patent Literature | C2081-7048WO_International_Search_Report.PDF | 412030<br>1e10ece4e8db649487bf5c95fdfaeff66a2ebd9c | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 22 | Non Patent Literature | C2081-7047WO.PDF | 528404<br>307ecd9eb56cbd32670a7a9b62eb6fe5f980e2d4 | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 23 | Non Patent Literature | C2081-7050WO_Search_Report.PDF | 448679<br>39097ec793c31adf1a9f96f584faa8d247268771 | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 24 | Non Patent Literature | International_Search_Report_C2081-7051WO.PDF | 394355<br>1bbae7474b320a7f9efab9e91dd248798ab9b657 | no | 13 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 25 | Non Patent Literature | C2081-7019WO_International_Search_Report_for_PCTUS1040486_dated_090110.PDF | 832837<br>109313ae7d8b5c9e2558bd85b0fb1eda13b3a555 | no | 12 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 26 | Non Patent Literature | E_F__C2081-7022WO_PCT_ISA_220_PCT_ISA_210_AND_PCT_ISA_237_MARCH_17_2011.PDF | 972730<br>03b8d2656e0e5772677a8dd2848088f9dc15fecf | no | 23 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 27 | Non Patent Literature | EF_4-28-11_C2081-7033WO_INTERNATIONAL_SEARCH_REPORT.PDF | 138179<br>ed940e47a173ee08225b87c4cce68a75e7d4360b | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 28 | Non Patent Literature | E_F__C2081-7021WO_PCT_ISA_220_APRIL_7_2011.PDF | 1581651<br>beca5909dfbe7439d05e25f8fad90b488910681e | no | 22 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 29 | Non Patent Literature | C2081-7035WO_search_report.PDF | 283651<br>eeaed15cec44bea8ada3f6691c7699d065baca0b | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 30 | Non Patent Literature | E_F__C2081-7031WO_PCT_ISA_210_PCT_ISA_220_AND_PCT_ISA_237_OCTOBER_5_2011.PDF | 7941911<br>47850547bd1a40c20d15c85a12c383d30655b956 | no | 172 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 31 | Non Patent Literature | C2081-7054WO_search_report.PDF | 608813<br>3eaa65838ecc38c0bc12dfe6d9ff69df29e31892 | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 32 | Non Patent Literature | kim_et_al.PDF | 1598522<br>e5406dc485ffb15995293b66837f5c534b5bb677 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 33 | Non Patent Literature | 1741697_1-Kim_et_al.PDF | 1170308<br>e2c09410c96b20fea3d1b2b2d0da742d42e66823 | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 34 | Non Patent Literature | NPL_-_Kranendijk_-_IDH2_Mutations_in_Patients_with_D-2-Hydroxyglutaric_Aciduria.PDF | 182819<br>11f6f66e7f726d821685d6bd999d3ddb663cc4c2 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 35 | Non Patent Literature | Parsons_et_al.PDF | 3758212<br>7cc86acd4ad99c230f49064aa1890dd87d926c61 | no | 23 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 36 | Non Patent Literature | Popovici_Muller.PDF | 892868<br>07c24ca25344969b37233221c748d0fe4244b0fe | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 37 | Non Patent Literature | Pubchem_4078245.PDF | 125668<br>1a97f197b223ebb8fa1c3438ae8f49c9698c1e6a | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 38 | Non Patent Literature | PubChem_4854170.PDF | 119693<br>070bdbf4b8cc444aabda56470c4a39d03581ecff | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 39 | Non Patent Literature | C2081-7028EP_ADVANCE_ACCESS_PUBLICATION_MAY_30_2010.PDF | 1082594<br>d8628e3680113ed958fb4c728b3c32851576d20f | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 40 | Non Patent Literature | C2081-7028EP_SCIENCEMAG_ARTICLE_SEPTEMBER_9_2013.PDF | 852853<br>acdb76bc672d7e0b8449fc9bc635a36ed8d2557e | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 41 | Non Patent Literature | chemical_journal_of_armenia.PDF | 86549<br>cb3490bc52651e1330e8b929aee12d62433b0319 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 42 | Non Patent Literature | NPL_-_Sonoda_-_Analysis_of_IDH1_and_IDH2_mutations_in_Japanese_glioma_patients.PDF | 490149<br>3f33697ae1ce54848ba86202cec498342953a065 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 43 | Non Patent Literature | 1023444-33-8.PDF | 17130<br>55b6df324cb93de7708b7a9776412 8f3d1ade6dc | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 44 | Non Patent Literature | 1090629-29-0.PDF | 17060<br>15666ba66341db0f02d768d31f1fd726dd42682c | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 45 | Non Patent Literature | 134538-28-6.PDF | 24631<br>f95e260864d00b7822ec0e55893cfc1bec5a6e51 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 46 | Non Patent Literature | 134538-29-7.PDF | 24630<br>5da3cb33f3d650ae02b9ca9325b0fc0acd2e62c1 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 47 | Non Patent Literature | 134538-30-0.PDF | 26663<br>abdc845132aa4d279f7df7ba2a8ad16ed426a3be | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 48 | Non Patent Literature | 134538-31-1.PDF | 26667<br>131912ee32bc14bc01e1acbbde1be253c991a483 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 49 | Non Patent Literature | 713505-78-3.PDF | 16860<br>34f61363078ac821ac73a3560ed253b32e08543d | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 50 | Non Patent Literature | 847757-57-7.PDF | 16857<br>c5d9cec1d28174f4233d5b2a4754e41231c79a45 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 51 | Non Patent Literature | 1032450-21-7.PDF | 14132<br>d680e16c64714f9a139971274264aac513a00a46 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 52 | Non Patent Literature | 1038821-72-5.PDF | 14612<br>e94f25f0911bd3c839b5e2325abb9c4fa326271d | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 53 | Non Patent Literature | Struys_et_al.PDF | 82435<br>7d95ee1ecb94c5d5ac3d30a16be21149f83c0f94 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 54 | Non Patent Literature | L68339PCEP_ESR.PDF | 151048<br>686c84efaec4d060ecb0003bb6ea607ae51752e7 | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 55 | Non Patent Literature | C2081-7019EP_Supplementary_Search_Report_for_EP10794668_Mailed_101812.PDF | 332557<br>3332caf50f9c2417e1dd8c9905942c2486426a1a | no | 10 |
| **Warnings:** | | | | | |
| The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing | | | | | |
| **Information:** | | | | | |
| 56 | Non Patent Literature | Wang_et_al.PDF | 667002<br>e21f911e059bee6f38117b6b798f929cc809d2ba | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 57 | Non Patent Literature | NPL_-_Ward_-_The_Common_Feature_of_Leukemia-Associated_IDH1_and_IDH2_Mutations_Is_a_Neomor.PDF | 2004901<br>abcaf7c192837b6bd594bbbd78cec2bd513b16dd | no | 23 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 58 | Non Patent Literature | 13-05-08_International_Search_Report_C2081-7050WOPPCUS13199.PDF | 474273<br>107b71db3fb0e9205f37758b52ab1b18baa7cf74 | no | 16 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 59 | Applicant Response to Pre-Exam Formalities Notice | C2081_701320_Resp_to_Missing_Parts.pdf | 20030<br>dd02c3a3470b32ec6e98594e51191f14e5bd9a5c | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 60 | Extension of Time | Extension_of_Time.pdf | 26484<br>2975e5bbb212f7c2bd25868cf3fb446bd31b4a61 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 61 | Fee Worksheet (SB06) | fee-info.pdf | 42003<br>95ebc0cd1f221ab4049d0e19ea5ff848ab6e243e | no | 2 |

| Warnings: | |
|---|---|
| Information: | |
| Total Files Size (in bytes): | 37653196 |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE



# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | | | | | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

**U.S.PATENT APPLICATION PUBLICATIONS** Remove

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | | | | | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | | | | | | | ☐ |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 1 | STN File CA, Registry Number 1090629-29-0, entered STN on December 28, 2008, Chemical Abstracts Index Name "Benzenesulfonamide, 3-[[4-[(2,5-dimethoxyphenyl)methyl]-1-piperazinyl]carbonyl]-N-(4-methoxyphenyl)-4-methyl-" | ☐ |
| | 2 | STN File CA, Registry Number 134538-28-6, entered STN on June 28, 1991, Chemical Abstracts Index Name "1H-Pyrano[3,4-c]pyridine-5-carbonitrile, 3,4-dihydro-3,3-dimethyl-6-[4-(1-oxobutyl)-1-piperazinyl]-8-phenyl-", disclosed in Paronikyan et al. Armyanskii Khimicheskii Zhurnal, 1990, Vol 43, No.8 | ☐ |
| | 3 | STN File CA, Registry Number 134538-29-7, entered STN on June 28, 1991, Chemical Abstracts Index Name "1H-Pyrano[3,4-c]pyridine-5-carbonitrile, 3,4-dihydro-3,3-dimethyl-6-[4-(2-methyl-1-oxopropyl)-1-piperazinyl]-8-phenyl-", disclosed in Paronikyan et al. Armyanskii Khimicheskii Zhurnal, 1990, Vol 43, No.8 | ☐ |
| | 4 | STN File CA, Registry Number 134538-30-0, entered STN on June 28, 1991, Chemical Abstracts Index Name "1H-Pyrano[3,4-c]pyridine-5-carbonitrile, 6-(4-benzoyl-1-piperazinyl)-3,4-dihydro-3,3-dimethyl-8-phenyl-", disclosed in Paronikyan et al. Armyanskii Khimicheskii Zhurnal, 1990, Vol 43, No.8 | ☐ |
| | 5 | STN File CA, Registry Number 134538-31-1, entered STN on June 28, 1991, Chemical Abstracts Index Name "1H-Pyrano[3,4-c]pyridine-5-carbonitrile, 6-[4-(2-furanylcarbonyl)-1-piperazinyl]-3,4-dihydro-3,3-dimethyl-8-phenyl-", disclosed in Paronikyan et al. Armyanskii Khimicheskii Zhurnal, 1990, Vol 43, No.8 | ☐ |
| | 6 | STN File CA, Registry Number 713505-78-3, entered STN on July 21, 2004, Chemical Abstracts Index Name "1-Piperazinecarboxylic acid, 4-[4-methyl-3-[(phenylamino)sulfonyl]benzoyl]-, ethyl ester" | ☐ |
| | 7 | STN File CA, Registry Number 847757-57-7, entered STN on April 1, 2005, Chemical Abstracts Index Name "Benzenesulfonamide, 3-[[4-(1,3-benzodioxol-5-ylmethyl)-1-piperazinyl]carbonyl]-N-(4-ethoxyphenyl)-N,4-dimethyl-" or "Piperazine, 1-(1,3-benzodioxol-5-ylmethyl)-4-[5-[[(4-ethoxyphenyl)methylamino]sulfonyl]-2-methylbenzoyl]-" | ☐ |
| | 8 | STN REGISTRY, L23 ANSWER 2 OF 3 (CAS NUMBER: 1032450-21-7), Database: ASINEX Ltd.,Entered STN: 03 Jul2008 (03. 07. 2008) | ☐ |
| | 9 | STNREGISTRY. L23 ANSWER 1 OF 3 (CAS NUMBER: 1038821-72-5),Database: ChemDB (University of California Irvine), Entered STN: 05 Aug. 2008 (05. 08. 2008) | ☐ |
| | 10 | STRUYS et al, Investigations by mass isotopomer analysis of the formation of D-2-hydroxyglutarate by cultured lymphoblasts from two patients with D-2-hydroxyglutaric aciduria, FEBS letters 92004 volume 557, pages 115-120 | ☐ |
| | 11 | STRUYS et al. "Mutations in the D-2-hydroxyglutarate dehydrogenase gene cause D-2-hydroxyglutaric aciduria" American Journal of Human Genetics, 2005. 76:358-360 | ☐ |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 12 | Supplementary European Search Report for EP Application No. 10825707.2 dated June 28, 2013 | ☐ |
| | 13 | Supplementary Search Report for EP10794668 Mailed 10/18/12. | ☐ |
| | 14 | Supplimentary European Search Report for EP 10751525 Mailed December 14, 2012. | ☐ |
| | 15 | THOMPSON, "Metabolic Enzymes as Oncogenes or Tumor Suppressors." The New England 18-22 Journal of Medicine, 19 February 2009, Vol 360, No 8, pp 813-815; pg 813, pg 815, col 1; Fig 1. | ☐ |
| | 16 | WANG et al. "A novel ligand N,N?-di(2-pyridyl)-2,4-diamino-6-phenyl-1,3,5-triazine (dpdapt) and its complexes: [Cu (dpdapt)Cl2] and [Cu(dpdapt)(NO3)(H2O)] · NO3 · H2O" Polyhedron, 2006. Vol 25, Issue 1. pp 195-202 | ☐ |
| | 17 | Ward, Patrick S, "The Common Feature of Leukemia-Associated IDH1 and IDH2 Mutations Is a Neomorphic Enzyme Activity Converting [alpha]-Ketoglutarate to 2-Hydroxyglutarate" Cancer cell, Vol:17,Nr:3,Page(s):225 - 234, 2010. | ☐ |
| | 18 | WATANABE et al., "IDH1 Mutations Are Early Events in the Development of Astrocytomas and Oligodendrogliomas". American Journal of Pathology, April 2009 (published online 26 February (2009), Vol 174, No 4, pp 1149-1153; Abstract, pg 1150, col 1. | ☐ |
| | 19 | Written Opinion for PCT/US2010/027253 mailed 08/19/10. | ☐ |
| | 20 | Written Opinion of International Search Authority for PCT/CN2013/000009 dated April 18, 2013 | ☐ |
| | 21 | Written Opinion of Search Authority for PCT/US2010/53623 dated January 18, 2011 | ☐ |
| | 22 | Written Opinion of the International Searching Authority for PCT/US2011/067752 dated March 5, 2012 | ☐ |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 23 | YAN et al., "IDH1 and IDH2 Mutations in Gliomas." The New England Journal of Medicine, 19 18-22 February 2009, Vol 360, No. 8, pp 765-73. | ☐ |
| | 24 | ZHAO ET AL: "Glioma-derived mutations in IDH1 dominantly inhibit IDH1 catalytic activity and induce HIF-1alpha", SCIENCE, vol. 324, no. 5924, 10 April2009 (2009-04-10), pages 261-265 | ☐ |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| Signature | /Asimina T. Georges Evangelinos/ | Date (YYYY-MM-DD) | 2014-03-12 |
|---|---|---|---|
| Name/Print | Asimina T. Georges Evangelinos | Registration Number | 66888 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE



**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 13939519 |
| Filing Date | 2013-07-11 |
| First Named Inventor | Leonard Luan C Dang |
| Art Unit | N/A |
| Examiner Name | Not Yet Assigned |
| Attorney Docket Number | C2081-701320 |

**U.S.PATENTS** Remove

| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 5834485 | | 1998-11-10 | Dyke et al. | |
| | 2 | 5965559 | | 1999-10-12 | Faull et al. | |
| | 3 | 5984882 | | 1999-11-16 | Rosenschein et al. | |
| | 4 | 6313127 | | 2001-11-06 | Waterson et al. | |
| | 5 | 6399358 | | 2002-06-04 | Williams et al. | |
| | 6 | 6723730 | | 2004-04-20 | Bakthavatchalam et al. | |
| | 7 | 6979675 | | 2005-12-27 | Tidmarsh | |
| | 8 | 7173025 | | 2007-02-06 | Stocker et al. | |

If you wish to add additional U.S. Patent citation information please click the Add button. Add

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| U.S.PATENT APPLICATION PUBLICATIONS | | | | | | Remove |
|---|---|---|---|---|---|---|
| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
| | 1 | 20030095958 | | 2003-05-22 | Bhisetti et al. | |
| | 2 | 20030109527 | | 2003-06-12 | Jin et al. | |
| | 3 | 20030207882 | A1 | 2003-11-06 | Stocker et al. | |
| | 4 | 20040067234 | | 2004-04-08 | Einat et al. | |
| | 5 | 20040248221 | | 2004-12-09 | Stockwell | |
| | 6 | 20060281122 | | 2006-12-14 | Bryant et al. | |
| | 7 | 20080300208 | | 2008-12-04 | Einat et al. | |
| | 8 | 20090093526 | | 2009-04-09 | Miller et al. | |
| | 9 | 20100331307 | | 2010-12-30 | Salituro et al. | |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 10 | 20120121515 | | 2012-05-17 | Dang et al. | |
| | 11 | 20120164143 | | 2012-06-28 | TEELING et al. | |
| | 12 | 20130035329 | | 2013-02-07 | Saunders et al. | |

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

**FOREIGN PATENT DOCUMENTS** Remove

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] i | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | 0384228 | EP | A1 | 1990-08-29 | Dainippon Pharmaceutical Co., Ltd | | ☐ |
| | 2 | 0385237 | EP | A2 | 1990-09-05 | Dainippon Pharmaceutical Co., Ltd | | ☐ |
| | 3 | 11158073 | JP | | 1999-06-15 | Takeda Chemical Industries LTD | | ☒ |
| | 4 | 2001016097 | WO | A1 | 2001-03-08 | Sugen, Inc | | ☐ |
| | 5 | 2004/073619 | WO | A2 | 2004-09-02 | Smithkline Beecham Corp | | ☐ |
| | 6 | 2004/074438 | WO | A2 | 2004-09-02 | Smithkline Beecham Corp | | ☐ |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 7 | 2006-038594 | WO | A1 | 2006-04-13 | Ono Pharmaceutical Co et al. | | ☐ |
| | 8 | 2006070198 | WO | A1 | 2006-07-06 | Astex Therapeutics Ltd | | ☐ |
| | 9 | 2007023186 | WO | A1 | 2007-03-01 | Applied Research Systems et al. | | ☐ |
| | 10 | 2008/050168 | WO | A1 | 2008-05-02 | Ritcher Gedeon Nyrt et al. | | ☐ |
| | 11 | 2008131547 | WO | A1 | 2008-11-06 | Prometic Biosciences Inc | | ☐ |
| | 12 | 2009013126 | WO | A1 | 2009-01-29 | Nerviano Medical Sciences Srl | | ☐ |
| | 13 | 2009150248 | WO | A1 | 2009-12-17 | Cytomics Systems | | ☐ |
| | 14 | 2010/028099 | WO | A1 | 2010-03-11 | Univ Johns Hopkins | | ☐ |
| | 15 | 2010007756 | WO | A1 | 2010-01-21 | Shionogi & Co., Ltd | | ☒ |
| | 16 | 2010105243 | WO | A1 | 2010-09-16 | Agios Pharmaceuticals, Inc | | ☐ |
| | 17 | 2010144338 | WO | A1 | 2010-12-16 | Abraxis Bioscience, Llc | | ☐ |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 18 | 2011/072174 | WO | A1 | 2011-06-16 | Agios Pharmaceuticals, Inc | | ☐ |
| | 19 | 2011002817 | WO | A1 | 2011-01-06 | Agios Pharmaceuticals, Inc | | ☐ |
| | 20 | 201105210 | WO | A1 | 2011-01-13 | Milux Holding Sa [lu] | | ☐ |
| | 21 | 2012/009678 | WO | A1 | 2012-01-19 | Agios Pharmaceuticals, Inc | | ☐ |
| | 22 | 2012/009678 | WO | A1 | 2012-01-19 | Agios Pharmaceuticals, Inc | | ☐ |
| | 23 | 2735127 | FR | A1 | 1996-12-13 | Pf Medicament | | ☐ |
| | 24 | 4099768 | JP | | 1992-03-31 | Dainippon Seiyaku | | ☒ |
| | 25 | 9291034 | JP | A | 1997-11-11 | Yoshitomi Pharmaceuticals Industries, Ltd. | | ☒ |
| | 26 | 97/28129 | WO | A1 | 1997-08-07 | Zeneca Ltd et al. | | ☐ |

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

**NON-PATENT LITERATURE DOCUMENTS** Remove

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T5 |
|---|---|---|---|

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 1 | AGHILI et al. "Hydroxyglutaric aciduria and malignant brain tumor: a case report and literature review", Journal of Neuroncology, 2008. 91:233-236 | ☐ |
| | 2 | BALSS, "Analysis of the IDH1 codon 132 mutation in brain tumors", Acata Neuropathol (2008) volume 116, pages 597-602. | ☐ |
| | 3 | BENNER et al, "Evolution, language and analogy in functional genomics", Trends in Genetics (2001) volume 17, pages 414-418. | ☐ |
| | 4 | BLEEKER et al., "IDH1 mutations at residue p.R132 (IDH1 (R132)) occur frequently in high-grade 18-22 gliomas but not in other solid tumors." Hum Muta1., January 2009, Vol 30, No 1, pp 7-11; | ☐ |
| | 5 | COCCO et al. "Synthesis of Triflouromethylated Pyridinecarbonitriles" Journal of Heterocyclic Chemistry, 1995. Volume 32 pp 543-545 | ☐ |
| | 6 | DANG et al., "Cancer-associated IDH1 mutations produce 2-hydroxyglutarate." Nature, 10 29-32 December 2009, Vol 462, No 7274, pp 739-744. | ☐ |
| | 7 | Dang, Lenny, " Cancer-associated IDH1 mutations produce 2-hydroxyglutarate", Nature, Vol:462,Nr:7274,Page(s):739 - 744, 2009. | ☐ |
| | 8 | EP Search Report & Written Opinion for EP 10825706 Dated 03/20/13 | ☐ |
| | 9 | European Search Report for Application No. 10751525.6 dated 12/14/2012 | ☐ |
| | 10 | Eurpoean Search Report for EP Application No. 11763425.3 dated September 23, 2013 | ☐ |
| | 11 | HARTMANN et al. "Type and Frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1010 diffuse gliomas" Acta Neuropathologica (2009) 118: 469-474 | ☐ |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 12 | HOLMES et al, 750 MHz 1H NMR spectroscopy characterisation of the complex metabolic pattern of urine from patients with inborn errors of metabolism: 2-hydroxyglutaric aciduria and maple syrup urine disease., Journal of Pharmaceutical and Biomedical Analysis (1997) volume 15, pages 1647-1659 | ☐ |
| | 13 | International Preliminary Report for related application No. PCT/US2010/059778 dated June 12, 2012 | ☐ |
| | 14 | International Preliminary Report on Patentability for PCT/CN2012/000841 dated December 17, 2013 | ☐ |
| | 15 | International Preliminary Report on Patentability for PCT/CN2012/077096 dated December 17, 2013 | ☐ |
| | 16 | International Preliminary Report on Patentability for PCT/US2010/027253 mailed 09/13/11. | ☐ |
| | 17 | International Preliminary Report on Patentability for PCT/US2010/040486 dated 1/12/12 | ☐ |
| | 18 | International Preliminary Report on Patentability for PCT/US2010/053623 dated April 24, 2012 | ☐ |
| | 19 | International Preliminary Report on Patentability for PCT/US2010/053624 dated 4/7/2011 | ☐ |
| | 20 | International Preliminary Report on Patentability for PCT/US2011/030692 dated October 2, 2012 | ☐ |
| | 21 | International Preliminary Report on Patentability for PCT/US2011/067752 dated April 11, 2013 | ☐ |
| | 22 | International Search Report & Written Opinion for PCT/CN2013/070755 dated April 25, 2013 | ☐ |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 23 | International Search Report for PCT/2011/030692 dated 7/27/2011 | ☐ |
| | 24 | International Search Report for PCT/CN2012/000841 dated September 27, 2012 | ☐ |
| | 25 | International Search Report for PCT/CN2012/077096 dated 10/4/2012 | ☐ |
| | 26 | International Search Report for PCT/CN2013/000009 dated April 18, 2013 | ☐ |
| | 27 | International Search Report for PCT/CN2013/000068 dated 04/25/13. | ☐ |
| | 28 | International Search Report for PCT/US10/040486 dated September 1, 2010. | ☐ |
| | 29 | International Search Report for PCT/US2010/027253 mailed 08/19/10. | ☐ |
| | 30 | International Search Report for PCT/US2010/059778 dated 03/17/11. | ☐ |
| | 31 | International Search Report for PCT/US2010/53623 dated January 18, 2011 | ☐ |
| | 32 | International Search Report for PCT/US2010053624 dated 4/7/2011 | ☐ |
| | 33 | International Search Report for PCT/US2011/067752 dated February 22, 2012 | ☐ |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 34 | International Search Report for PCT/US2011044254 dated 5/10/2011 | ☐ |
| | 35 | International Search Report for PCT/US2013/064601 dated February 24, 2014 | ☐ |
| | 36 | JENNINGS et al, Expression and mutagenesis of mammalian cytosolic NADP+-specific isocitrate dehydrogenase, Biochemistry (1997)volume 36, pages 13743-13747 | ☐ |
| | 37 | KIM et al " Ser95, Asn97, and Thr78 are important for the catalytic function of porcine NADP-dependent isocitrate dehydrogenase" Protein Science (2005) 14: pp140-147 | ☐ |
| | 38 | KIM et al. "Identification and Functional Characterization of a Novel, Tissue-specific NAD1-dependent Isocitrate Dehydrogenase b Subunit Isoform" JBC. 24 December 1999, Vol 274 No. 52 pages 36866-36875 | ☐ |
| | 39 | Kranendijk, Martijn, "IDH2 Mutations in Patients with D-2-Hydroxyglutaric Aciduria" Sciences, Vol:330,Page(s):336, 2010. | ☐ |
| | 40 | MAY et al, How many species are there on earth, Science (1988) volume 241, page 1441 | ☐ |
| | 41 | PARSONS et al. "An Integrated Genomic Analysis of Human Glioblastoma Multiforme" Science Vol 321 (2008) pp 1807-1812 and Supplemental Data | ☐ |
| | 42 | POLLARD et al, "Cancer. Puzzling patterns of predisposition." Science. 10 April 2009, Vol 324, 1-5,15-16, 18-22,35-38 No 5924, pp 192-194. | ☐ |
| | 43 | POPOVICI-MULLER, Janeta et al. Discovery of the First Potent Inhibitors of Mutant IDH1 That Lower Tumor2-HG in Vivo. ACS Medicinal Chemistry Letters. 17 Sep. 2012 (17. 09. 2012), vol. 3, no. 10, 850-855 | ☐ |
| | 44 | PUBCHEM CID 4078245 [online]; September 13, 2005 [retrieved on February 4, 2012]; retrieved from http://pubchem.ncbi.nim.nih.gov/; 2d-structure | ☐ |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

| | | | |
|---|---|---|---|
| | 45 | PUBCHEM CID 4854170 [online]; September 17, 2005 [retrieved on February 4, 2012]; retrieved from http://pubchem.ncbi.nim.nih.gov/; 2d-structure | ☐ |
| | 46 | REITMAN et al. "Isocitrate Sehydrogenase 1 and 2 Mutations in Cancer: Alterations at a Crossroads of Cellular Metabolism" Journal of the National Cancer Institute, Vol. 102, No. 13, pp 932-941 (2010). | ☐ |
| | 47 | ROHLE et al. "An Inhibitor of Mutant IDH1 Delays Growth and Promotes Differentiation of Glioma Cells" Science, Vol. 340, No. 6132 pp 626-630 (2013) | ☐ |
| | 48 | SIRKANYAN, S.N. et al "Synthesis of new derivatives of piperazine-substituted pyrano[3,4-c]pyridines. Hayastani Kimiakan Handes 2009, Vol. 62, No 3-4 pp 378-385. English Abstract Only. | ☐ |
| | 49 | Sonoda, Yukihiko, " Analysis of IDH1 and IDH2 mutations in Japanese glioma patients" Cancer Science, Vol:100,Nr:10,Page(s):1996 - 1998, 2009. | ☐ |
| | 50 | STN File CA, Registry Number 1023444-33-8, entered STN on May 29, 2008, Chemical Abstracts Index Name "Benzenesulfonamide, 3-[[4-(1,3-benzodioxol-5-ylmethyl)-1-piperazinyl]carbonyl]-N-(4-butylphenyl)-4-methyl-" | ☐ |

If you wish to add additional non-patent literature document citation information please click the Add button Add

**EXAMINER SIGNATURE**

| Examiner Signature | | Date Considered | |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 13939519 |
| | Filing Date | 2013-07-11 |
| | First Named Inventor | Leonard Luan C Dang |
| | Art Unit | N/A |
| | Examiner Name | Not Yet Assigned |
| | Attorney Docket Number | C2081-701320 |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| Signature | /Asimina T. Georges Evangelinos/ | Date (YYYY-MM-DD) | 2014-03-12 |
|---|---|---|---|
| Name/Print | Asimina T. Georges Evangelinos | Registration Number | 66888 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Docket No.: C2081-701320
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Leonard Luan C Dang et al.

Application No.: 13/939,519 | Confirmation No.: 2110

Filed: July 11, 2013 | Art Unit: N/A

For: METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS | Examiner: Not Yet Assigned

## INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents

Dear Madam:

Pursuant to 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a first Office Action on the merits as far as is known to the undersigned (37 C.F.R. § 1.97(b)(3)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2). Copies of certain references cited in the attached form PTO/SB/08 are not supplied because they were previously cited by or submitted to the Office in a prior application number and relied upon in this application for an earlier filing date under 35 U.S.C. 120.

Applicant would like to bring to the Examiner's attention the following U.S. applications that may contain subject matter related to this application:

| Application No. | Filing Date | Docket (C2081) |
|---|---|---|
| 14/126,791 | 18-Jun-2012 | 7047US |
| 14/126,763 | 18-Jun-2012 | 7048US |

| Publication No. | Filing Date | Docket (C2081) |
|---|---|---|
| US-2013-0183281-A1 | 20-Apr-2012 | 703320 |
| US-2012-0121515-A1 | 12-Mar-2010 | 7013US |
| US-2013-0316385-A1 | 14-Sep-2012 | 702120 |
| US-2013-0035329-A1 | 08-Jun-2012 | 702220 |
| US-2013-0197106-A1 | 31-Mar-2011 | 7028US |
| US-2013-0184222-A1 | 15-Jul-2011 | 7031US |
| US-2013-0190287-A1 | 07-Jan-2013 | 705010 |
| US-2013-0190249-A1 | 18-Jan-2013 | 705110 |
| US-2013-0288284-A1 | 14-Sep-2012 | 703321 |

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. § 1.56(a) exists. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98 and the Examiner is respectfully requested to consider the listed references.

No fee is believed to be due. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 50/2762, under Order No. C2081-701320.

Dated: March 12, 2014

Respectfully submitted,

By: /Asimina T. Georges Evangelinos/
Asimina T. Georges Evangelinos
Registration No.: 66,888
LANDO & ANASTASI LLP
One Main Street Suite 1100
Cambridge, Massachusetts 02142
(617) 395-7000
Attorney for Applicant

**DECLARATION FOR PATENT APPLICATION**

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, titled METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS , or

☒ United States application or PCT International application number 13/939,519 filed on 07/11/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby state that I have reviewed and understand the contents of the application, including the claims.

I acknowledge the duty to disclose all information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that any willful false statements made in this declaration are punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Leonard Dang 10.08.13

**Inventor's signature** **Date**

Full legal name of original or original joint inventor: Leonard L. Dang

**DECLARATION FOR PATENT APPLICATION**

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, titled METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS , or

☒ United States application or PCT International application number 13/939,519 filed on 07/11/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby state that I have reviewed and understand the contents of the application, including the claims.

I acknowledge the duty to disclose all information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that any willful false statements made in this declaration are punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

V Fantin 10-02-13

**Inventor's signature** **Date**

Full legal name of original or original joint inventor: Valeria Fantin

**DECLARATION FOR PATENT APPLICATION**

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, titled METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS , or

☒ United States application or PCT International application number 13/939,519 filed on 07/11/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby state that I have reviewed and understand the contents of the application, including the claims.

I acknowledge the duty to disclose all information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that any willful false statements made in this declaration are punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

[signature], PhD 30 NOV 13

**Inventor's signature** **Date**

Full legal name of original or original joint inventor: Stefan Gross

**DECLARATION FOR PATENT APPLICATION**

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, titled METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS , or

☒ United States application or PCT International application number 13/939,519 filed on 07/11/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby state that I have reviewed and understand the contents of the application, including the claims.

I acknowledge the duty to disclose all information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that any willful false statements made in this declaration are punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

9/30/2013

**Inventor's signature** **Date**

Full legal name of original or original joint inventor: Hyun G. Jang

**DECLARATION FOR PATENT APPLICATION**

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, titled METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS , or

☒ United States application or PCT International application number 13/939,519 filed on 07/11/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby state that I have reviewed and understand the contents of the application, including the claims.

I acknowledge the duty to disclose all information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that any willful false statements made in this declaration are punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

9/30/2013

**Inventor's signature** **Date**

Full legal name of original or original joint inventor: Hyun G. Jang

**DECLARATION FOR PATENT APPLICATION**

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, titled METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS , or

☒ United States application or PCT International application number 13/939,519 filed on 07/11/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby state that I have reviewed and understand the contents of the application, including the claims.

I acknowledge the duty to disclose all information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that any willful false statements made in this declaration are punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Shengfang Jin 10-1-2013

**Inventor's signature** **Date**

Full legal name of original or original joint inventor: Shengfang Jin

**DECLARATION FOR PATENT APPLICATION**

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, titled METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS , or

☒ United States application or PCT International application number 13/939,519 filed on 07/11/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby state that I have reviewed and understand the contents of the application, including the claims.

I acknowledge the duty to disclose all information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that any willful false statements made in this declaration are punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Francesco G. Salituro 10-7-2013

**Inventor's signature** **Date**

Full legal name of original or original joint inventor: Francesco G. Salituro

**DECLARATION FOR PATENT APPLICATION**

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, titled METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS , or

☒ United States application or PCT International application number 13/939,519 filed on 07/11/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby state that I have reviewed and understand the contents of the application, including the claims.

I acknowledge the duty to disclose all information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that any willful false statements made in this declaration are punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

10.01.13

**Inventor's signature** **Date**

Full legal name of original or original joint inventor: Jeffrey O. Saunders

**DECLARATION FOR PATENT APPLICATION**

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, titled METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS , or

☒ United States application or PCT International application number 13/939,519 filed on 07/11/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby state that I have reviewed and understand the contents of the application, including the claims.

I acknowledge the duty to disclose all information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that any willful false statements made in this declaration are punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

10.02.13

**Inventor's signature** **Date**

Full legal name of original or original joint inventor: Shin-San M. Su

**DECLARATION FOR PATENT APPLICATION**

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, titled METHODS AND COMPOSITIONS FOR CELL-PROLIFERATION-RELATED DISORDERS , or

☒ United States application or PCT International application number 13/939,519 filed on 07/11/2013 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby state that I have reviewed and understand the contents of the application, including the claims.

I acknowledge the duty to disclose all information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that any willful false statements made in this declaration are punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

10.01.13

**Inventor's signature** **Date**

Full legal name of original or original joint inventor: Katharine Yen

PCT/US2010/059778

**PATENT COOPERATION TREATY**

# ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

# PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

MCCARTY, Catherine, M.
Lando & Anastasi, LLP
One Main Street, Eleventh Floor
Cambridge, MA 02142
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
21 June 2012 (21.06.2012)

Applicant's or agent's file reference
C2081-7022WO

**IMPORTANT NOTICE**

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US2010/059778 | 09 December 2010 (09.12.2010) | 09 December 2009 (09.12.2009) |

Applicant
AGIOS PHARMACEUTICALS, INC. et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Nora Lindner

e-mail: pt03.pct@wipo.int

Form PCT/IB/326 (January 2004)

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>C2081-7022WO | **FOR FURTHER ACTION** | See item 4 below |
| International application No.<br>PCT/US2010/059778 | International filing date *(day/month/year)*<br>09 December 2010 (09.12.2010) | Priority date *(day/month/year)*<br>09 December 2009 (09.12.2009) |
| International Patent Classification (8th edition unless older edition indicated)<br>See relevant information in Form PCT/ISA/237 | | |
| Applicant<br>AGIOS PHARMACEUTICALS, INC. | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☒ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

| | |
|---|---|
| | Date of issuance of this report<br>12 June 2012 (12.06.2012) |
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br>Facsimile No. +41 22 338 82 70 | Authorized officer<br>Nora Lindner<br>e-mail: pt03.pct@wipo.int |

Form PCT/IB/373 (January 2004)

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
*(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

**FOR FURTHER ACTION**
See paragraph 2 below

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US2010/059778 | 09.12.2010 | 09.12.2009 |

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/495 A61K31/496 A61K31/506 A61K31/551 C07D243/08 C07D405/12 A61P35/00

Applicant
AGIOS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA: | Date of completion of this opinion | Authorized Officer |
|---|---|---|
| European Patent Office<br>P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk - Pays Bas<br>Tel. +31 70 340 - 2040<br>Fax: +31 70 340 - 3016 | see form PCT/ISA/210 | Hoff, Philippe<br>Telephone No. +31 70 340-3520 |

Form PCT/ISA/237 (Cover Sheet) (July 2009)

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☒ on paper

      ☒ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☒ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1, 3-12, 14, 17, 18(all partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1, 3-12, 14, 17, 18(all partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 2, 13(completely); 1, 3-8, 10-12(partially) |
| | No: | Claims | 15, 16(completely); 9, 14, 17, 18(partially) |
| Inventive step (IS) | Yes: | Claims | 2, 13(completely); 1, 3-8, 10-12(partially) |
| | No: | Claims | 15, 16(completely); 9, 14, 17, 18(partially) |
| Industrial applicability (IA) | Yes: | Claims | 2, 13, 15, 16(completely); 1, 3-12, 14, 17, 18(partially) |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**Box No. VI Certain documents cited**

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

**see form 210**

Re Item III

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Present claims 1,3-12,14,17,18 relate to an extremely large number of possible compounds. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds claimed, see examples.

The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the claims (PCT Guidelines 9.19 and 9.23).

The search of claims 1,3-12,14,17,18 was restricted to those claimed compounds which appear to be supported (see examples) and a generalisation of their structural formulae, namely compounds of formulas (I),(Ic),(II),(III),(IV) wherein at least one of D and D1 is $NR^c$ .

**No opinion will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).**

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1 WO 2004/074438 A2 (SMITHKLINE BEECHAM CORP [US]; JIN JIAN [US]; KERNS JEFFREY K [US]; SHI) 2 September 2004 (2004-09-02)

D2 WO 2004/073619 A2 (SMITHKLINE BEECHAM CORP [US]; JIN JIAN [US]; KERNS JEFFREY K [US]; WAN) 2 September 2004 (2004-09-02)

D3 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1 April 2005 (2005-04-01),
XP002626839,
Database accession no. 847757-57-7

D4 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 29 May 2008 (2008-05-29),
XP002626840,
Database accession no. 1023444-33-8

D5 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 21 July 2004 (2004-07-21),
XP002626841,
Database accession no. 713505-78-3

D6 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 28 December 2008 (2008-12-28),
XP002626842,
Database accession no. 1090629-29-0

D7 YAN HAI ET AL: "IDH1 and IDH2 mutations in gliomas.",
THE NEW ENGLAND JOURNAL OF MEDICINE 19 FEB 2009 LNKD-PUBMED:19228619,
vol. 360, no. 8, 19 February 2009 (2009-02-19), pages 765-773,
XP002626843,
ISSN: 1533-4406

D8 BALSS JOERG ET AL: "Analysis of the IDH1 codon 132 mutation in brain tumors",
ACTA NEUROPATHOLOGICA,
vol. 116, no. 6, December 2008 (2008-12), pages 597-602,
XP002626844,
ISSN: 0001-6322

D9 WO 2009/013126 A1 (NERVIANO MEDICAL SCIENCES SRL [IT]; LOMBARDI BORGIA ANDREA [IT]; MENIC) 29 January 2009 (2009-01-29)

D10 WO 2006/070198 A1 (ASTEX THERAPEUTICS LTD [GB]; BERDINI VALERIO [GB]; O'BRIEN MICHAEL ALI) 6 July 2006 (2006-07-06)

D11 FR 2 735 127 A1 (PF MEDICAMENT [FR]) 13 December 1996 (1996-12-13)

Claims 1-7 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 9,14-18 is not new in the sense of Article 33(2) PCT.

1.1 Document D1 discloses compounds of formula (Ic), not excluded from the scope of claim 9 by the proviso and wherein R1 is cycloalkylalkyl or aralkyl, A is naphthyl, D is NH and D1 is a bond (see tables 1,2; claims; examples).

Document D2 discloses compounds of formula (Ic), not excluded from the scope of claim 9 by the proviso and wherein R1 is cycloalkylalkyl, A is phenyl substituted with 1 or 2 R2 (R2 being alkyl, aryl, alkoxy), D is NH and D1 is a bond (examples; tables 1,2; claims).

Document D5 discloses a compound of formula (Ic), not excluded from the scope of claim 9 by the proviso and wherein R1 is acyl substituted with $-OR^a$ ($R^a$ is ethyl), A is phenyl, D is a bond and D1 is NH.

Document D6 discloses a compound of formula (Ic), not excluded from the scope of claim 9 by the proviso and wherein R1 is aralkyl, A is phenyl substituted with methoxy, D is a bond and D1 is NH.

Consequently, claim 9 lacks novelty over D1,D2,D5 and D6.

1.2 Document D3 discloses a compound of formulas (Ic) and (IV), not excluded from the scope of claims 9 and 14 by the proviso and wherein R1 is heteroarylalkyl, A is phenyl substituted with ethoxy, D is a bond and D1 is $NR^c$ , R3 is methyl.

Consequently, claims 9,14,15,17,18 lack novelty over D3.

1.3 Document D4 discloses a compound of formulas (Ic) and (IV), not excluded from the scope of claims 9 and 14 by the proviso and wherein R1 is heteroarylalkyl, A is phenyl substituted with alkyl, D is a bond and D1 is NH , R3 is methyl.

Consequently, claims 9,14-18 lack novelty over D4.

2. The subject-matter of claims 1-8, 10-13 seems however to be new and inventive and satisfies therefore the requirements of Articles 33(2) and (3) PCT.

2.1 None of the available prior art documents discloses the use of a compound of formula (I) in the treatment of a cancer characterized as having an IDH mutation. The compounds of claims 10-13 seem also to be new.

2.2 In the light of the prior art, the problem to be solved can be regarded as the provision of a new medicament for treating a cancer characterised by an IDH mutation.

Certain compounds of formula (I) have been disclosed in relation to the treatment of cancer (see D9-D11 and corresponding passages mentioned in the search report). However, tumors with IDH mutations have distinctive genetic and clinical characteristics (D7) and no indication were found in the prior art which would have led the skilled person to select a compound of formula (I) for treating this particular kind of cancer.

**Re Item VI**

**Certain documents cited**

The examination has been carried out assuming that the priority of the application is valid. However, attention is drawn to the fact that the documents which has been cited in the search report as "E/P" documents may become relevant in the national/regional examination phase.

Document WO 2011/002817 discloses compounds of claims 9-17.

Document WO 2010/105243 discloses the use of a compound of formula (I) for treating a cancer having an IDH mutation.

**PATENT COOPERATION TREATY**

# ADVANCE E-MAIL

# PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

From the INTERNATIONAL BUREAU

To:

NTD PATENT AND TRADEMARK AGENCY LIMITED
10th Floor, Block A, Investment Plaza
27 Jinrongdajie, Xicheng District
Beijing 100033
CHINE

| Date of mailing *(day/month/year)* | |
|---|---|
| 03 January 2014 (03.01.2014) | |
| Applicant's or agent's file reference<br>P2012873C | **IMPORTANT NOTICE** |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/CN2012/000841 | 18 June 2012 (18.06.2012) | 17 June 2011 (17.06.2011) |

Applicant
AGIOS PHARMACEUTICALS, INC. et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Lingfei Bai

e-mail: pt02.pct@wipo.int

Form PCT/IB/326 (January 2004)

**PATENT COOPERATION TREATY**

# PCT

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>P2012873C | **FOR FURTHER ACTION** | See item 4 below |
| International application No.<br>PCT/CN2012/000841 | International filing date *(day/month/year)*<br>18 June 2012 (18.06.2012) | Priority date *(day/month/year)*<br>17 June 2011 (17.06.2011) |
| International Patent Classification (8th edition unless older edition indicated)<br>See relevant information in Form PCT/ISA/237 | | |
| Applicant<br>AGIOS PHARMACEUTICALS, INC. | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☒ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

| | |
|---|---|
| | Date of issuance of this report<br>17 December 2013 (17.12.2013) |
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br>Facsimile No. +41 22 338 82 70 | Authorized officer<br>Lingfei Bai<br>e-mail: pt02.pct@wipo.int |

Form PCT/IB/373 (January 2004)

**PATENT COOPERATION TREATY**

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

100033

10th Floor, Block A Investment Plaza 27
Jinrongdajie,Xicheng District, Beijing 100033
China

NTD PATENT & TRADEMARK AGENCY LTD

# PCT

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

(PCT Rule 43 *bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 27 Sep. 2012 (27.09.2012) |
| Applicant's or agent's file reference: P2012873C | **FOR FURTHER ACTION** See paragraph 2 below |

| International application No. | International filing date(*day/month/year*) | Priority date (*day/month/year*) |
|---|---|---|
| PCT/CN2012/000841 | 18 Jun. 2012(18.06.2012) | 17 Jun. 2011(17.06.2011) |

International Patent Classification (IPC) or both national classification and IPC
See Supplemental Box

Applicant
AGIOS PHARMACEUTICALS,INC. et al.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No.II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No.VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No.VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of **3** months from the date of mailing of Form PCT/ISA/220 or before the expiration of **22** months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/CN | Date of completion of this opinion | Authorized officer |
|---|---|---|
| The State Intellectual Property Office, the P.R.China<br>6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088<br>Facsimile No. 86-10-62019451 | 10 Sep. 2012 (10.09.2012) | HAO,Peng<br>Telephone No.<br>(86-10)82246764 |

Form PCT/ISA/237(cover sheet)( July 2009)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/000841

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.
   ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application ,this opinion has been established on the basis of :

   a. a sequence listing filed or furnished

      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing

      ☐ contained in the applicant as filed
      ☐ filed together with the application in electronic form
      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/000841

**Box No.III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

This questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious),or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-3(part), 4, 5-21(part), 22-25

because:

☒ the said international application, or the said claims Nos. 22-25

relate to the following subject matter which does not require an international search (*specify*):

See Box No. II in PCT/ISA/210.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos.

are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 1-3(part), 4, 5-25(part) are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

See Box No. II in PCT/ISA/210.

☐ no international search report has been established for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule **13ter.1(a) or (b).**

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/000841

**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement:

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-3(part), 5-25(part) | YES |
| | Claims | NONE | NO |
| Inventive step (IS) | Claims | NONE | YES |
| | Claims | 1-3(part), 5-25(part) | NO |
| Industrial applicability (IA) | Claims | 1-3(part), 5-25(part) | YES |
| | Claims | NONE | NO |

2. Citations and explanations

The explanations of claim 6 with regard to novelty, inventive step or industrial applicability are made based on that claim 6 is a dependent claim of claim 5. (see Box No. VIII)

The explanations of claim 12 with regard to novelty, inventive step or industrial applicability are made based on its general scope. (see Box No. VIII).

Reference is made to the following document:

D1: WO 2010/007756 A1 (SHIONOGI & CO., LTD. et al.) 21 Jan. 2010 (21. 01. 2010)

**I. Novelty**

D1 discloses compounds with formula I especially with the structure of example 2-272 and example 2-343 which are used to treat cancer (see claims 1, 19-25, example 2-272, example 2-343 of description).

No relevant compounds falling into the scope of present claim 1 as defined that Y is $-N(R^5)-$ and $R^4$ is selected from –CN or $C(O)-O-C_1-C_4$ alkyl are disclosed by D1. Therefore, the present claim 1 is novel in the sense of Article 33(2) PCT. For the same reason, dependent claims 2-3, 5-19 and claims 20-25 comprising the compounds of claim 1 are also novel in the sense of Article 33(2) PCT.

**II. Inventive step**

For claim 1, D1 is considered as the closest prior art. The compound in D1 which is structurally closest to the presently claimed compounds is example 2-272 in table 6 of description. Said compound corresponds to a compound of present formula (I) in claim 1 wherein $R^2$=4-MeCONH-Ph, $R^{1b}$=H, $R^{1a}$=5-methylfuran-2-yl, $R^4$=CN, m=0, $R^5$=furan-2-yl-CO-. The difference between claim 1 and D1 is that $R^2$ in present claim 1 is phenyl which can be substituted by methyl or fluoro. Though the compounds in present claim 1 are said to be the inhibitors of IDH1 mutants, while the compounds in D1 are described as inhibitors of TTK protein kinase, both of them are used to treat cancer. Thus, the technical problem to be solved by the present claim can be seen in provision of alternative compounds for the treatment of cancer. D1 also discloses that $R^5$ (equal to $R^2$ in the present claim 1) in formula I could be substituted aryl group and the substitute could be methyl or halide (see paragraph [0123] of description and claim 1 in D1). Therefore, it appears obvious for a person skilled in the art to modify the compound of example 2-272 in D1 by changing 4-MeCONH-Ph into phenyl substituted by methyl or fluoro in order to acquire the subject matter of claim 1. Accordingly, claim 1 does not involve an inventive step in the sense of Article 33(3) PCT.

Claims 2-3, 5-19 further define claim 1. The additional technical feature of different groups is a customary option in the art. Therefore, claims 2-3, 5-19 do not involve an inventive step in the sense of Article 33(3) PCT.

Since D1 discloses example 2-272 as inhibitor of TTK protein kinase, pharmaceutical composition comprising this compound and its use in manufacture of a medicament for treating cancer, the present claims 20-21 for pharmaceutical compositions and claims 22-25 for use are not considered inventive and do not involve an inventive step in the sense of Article 33(3) PCT.

**III. Industrial applicability**

The subject matter of claims 1-3, 5-25 can be made or used in pharmaceutical industry, so the subject matter of claims 1-3, 5-25 meets the criteria of Article 33(4) PCT.

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/000841

**Box No. VII Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

1. Multiple dependent claims 18-19 refer to other multiple dependent claims, so claims 18-19 do not meet the requirements of Rule 6.4(a) PCT.

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/000841

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. The present claim 1 relates to an extremely large number of possible compounds. Support and disclosure in the sense of Article 6 and 5 PCT are to be found however for only a very small proportion of the compound claimed, (see exemplary compounds 100-829 on pages 24-95). Thus, claim 1 does not meet the criteria set out in Article 6 and 5 PCT. As the same reason, claims 2-25 do not meet the criteria set out in Article 6 and 5 PCT too.
2. Claim 6 is a dependent claim of claim 6, which renders the protection scope unclear. Thus, claim 6 does not meet the criteria set out in Article 6 PCT. The written opinion has been made based that claim 6 is a dependent claim of claim 5.
3. There is a bracket in claim 12, so claim 12 simultaneously involves a general scope and a preferred scope, which renders the protection scope of the said claim unclear. Thus, claim 12 does not meet the criteria set out in Article 6 PCT. The written opinion has been made based on the general scope.

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of : International Patent Classification (IPC) or both national classification and IPC

C07D 401/04 (2006.01) i

C07D 401/02 (2006.01) i

C07D 401/14 (2006.01) i

C07D 405/00 (2006.01) i

A61K 31/44 (2006.01) i

A61K 31/4427 (2006.01) i

A61P 35/00 (2006.01) i

**PATENT COOPERATION TREATY**

# ADVANCE E-MAIL

# PCT

From the INTERNATIONAL BUREAU

To:

NTD PATENT AND TRADEMARK AGENCY LIMITED
10th Floor, Block A, Investment Plaza
27 Jinrongdajie, Xicheng District
Beijing 100033
CHINE

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

| | |
|---|---|
| Date of mailing *(day/month/year)*<br>03 January 2014 (03.01.2014) | |
| Applicant's or agent's file reference<br>P2012874C | **IMPORTANT NOTICE** |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/CN2012/077096 | 18 June 2012 (18.06.2012) | 17 June 2011 (17.06.2011) |

Applicant
AGIOS PHARMACEUTICALS, INC. et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Lingfei Bai

e-mail: pt02.pct@wipo.int

**PATENT COOPERATION TREATY**

# PCT

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>P2012874C | **FOR FURTHER ACTION** | See item 4 below |
| International application No.<br>PCT/CN2012/077096 | International filing date *(day/month/year)*<br>18 June 2012 (18.06.2012) | Priority date *(day/month/year)*<br>17 June 2011 (17.06.2011) |
| International Patent Classification (8th edition unless older edition indicated)<br>See relevant information in Form PCT/ISA/237 | | |
| Applicant<br>AGIOS PHARMACEUTICALS, INC. | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

| | |
|---|---|
| | Date of issuance of this report<br>17 December 2013 (17.12.2013) |
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br>Facsimile No. +41 22 338 82 70 | Authorized officer<br>Lingfei Bai<br>e-mail: pt02.pct@wipo.int |

Form PCT/IB/373 (January 2004)

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

100033

10th Floor, Block A Investment Plaza 27
Jinrongdajie,Xicheng District, Beijing 100033
China

NTD PATENT & TRADEMARK AGENCY LTD

# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43 *bis*.1)

| | |
|---|---|
| Date of mailing (*day/month/year*) | 04 Oct. 2012 (04.10.2012) |
| Applicant's or agent's file reference: P2012874C | **FOR FURTHER ACTION** See paragraph 2 below |

| International application No. | International filing date (*day/month/year*) | Priority date (*day/month/year*) |
|---|---|---|
| PCT/CN2012/077096 | 18 Jun. 2012(18.06.2012) | 17 Jun. 2011(17.06.2011) |

International Patent Classification (IPC) or both national classification and IPC
See Supplemental Box

Applicant
AGIOS PHARMACEUTICALS, INC. et al.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No.II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No.VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No.VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of **3** months from the date of mailing of Form PCT/ISA/220 or before the expiration of **22** months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/CN | Date of completion of this opinion | Authorized officer |
|---|---|---|
| The State Intellectual Property Office, the P.R.China<br>6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088<br>Facsimile No. 86-10-62019451 | 17 Sep. 2012 (17.09.2012) | ZHAO, Zhenzhen<br>Telephone No.<br>(86-10) 62086358 |

Form PCT/ISA/237(cover sheet)( July 2009)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/077096

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application ,this opinion has been established on the basis of :

a. a sequence listing filed or furnished

☐ on paper
☐ in electronic form

b. time of filing or furnishing

☐ contained in the applicant as filed
☐ filed together with the application in electronic form
☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CN2012/077096

**Box No.III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

This questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious),or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 32-35

because:

☒ the said international application, or the said claims Nos. 32-35
relate to the following subject matter which does not require an international search (*specify*):

See PCT/ISA/210 Box No. II 1.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos.
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule **13ter.1(a) or (b).**

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No. PCT/CN2012/077096

**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement:

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 6-8, 11-13, 15-29, 31-35 | YES |
| | Claims | 1-5, 9-10, 14, 30 | NO |
| Inventive step (IS) | Claims | 6-8, 11-13, 15-29, 31-35 | YES |
| | Claims | 1-5, 9-10, 14, 30 | NO |
| Industrial applicability (IA) | Claims | 1-35 | YES |
| | Claims | NONE | NO |

2. Citations and explanations

This written opinion is established on the basis of subject matter anticipated reasonably, please see Box No. III and Box No. VIII for more details.

2.1 Reference is made to the following documents:

D1: SIRAKANYAN, S. N. et al. Synthesis of new derivatives of piperazine-substituted pyrano[3, 4- c]pyridines. Hayastani Kimiakan Handes 2009, Vol. 62, No. 3-4, pages 378-385, ISSN:1561-4190

D2: JP 9291034 A(Yoshitomi Pharmaceutical Industries, Ltd.) 11 Nov.1997 (11.11.1997)

D3: JP 4099768 A (Dainippon Seiyaku K. K.) 31 Mar.1992 (31. 03. 1992)

D4: EP 385237 A2 (Dainippon Pharmaceutical Co., Ltd.) 05 Sep. 1990 (05. 09. 1990)

D5: EP 384228 A1 (Dainippon Pharmaceutical Co., Ltd.) 29 Aug. 1990 (29. 08. 1990)

D6: CHEM ABSTRACT No. 115: 29158 & Paronikyan, E. G. et al. Synthesis and biological activity of 3-piperazinylpyrano[3,4-c]pyridines. Armyanskii Khimicheskii Zhurnal 1990, Vol. 43, No. 8, pages 518-23

2.2 Novelty

The present application claims compounds of formula (I), pharmaceutical compositions , and the use of the compositions in the manufacture of corresponding medicaments.

The compounds 4a, 4b, 4g, 4h, 4i disclosed in D1 (see page 379 of D1) have fallen into the scopes of claims 1-5, 9.

The compounds 37, 40, 43, 47, 49, 53-57, 59-63, 66-74 disclosed in D2 (see pages 16-23 of D2) have fallen into the scopes of claims 1, 4, 9-10.

See Supplemental Box

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Dependent claim 19 refers to claim 18, however, the definition of "$R^2$ is selected from ethyl" in claim 19 goes beyond the scope of "$R^2$" in claim 18. Therefore, claim 19 is unclear and does not comply with PCT Article 6.

Dependent claim 22 refers to claim 120, however, claim 120 does not exist. Therefore, claim 22 is unclear and does not comply with PCT Article 6.

Claim 28 does not define substituents of $R^{3a}$, $R^{3b}$, $R^{3c}$, $R^{3d}$ present in the formula of said claim. Thus claim 28 is unclear and does not comply with PCT Article 6.

This written opinion is established on the basis of subject matter anticipated reasonably, i.e., definition of $R^2$ in claim 19 can also be ethyl, and claim 22 refers to claim 20, and definitions of $R^{3a}$, $R^{3b}$, $R^{3c}$, $R^{3d}$ in claim 28 are the same as that in page 16 of the description.

**Supplemental Box**

In case the space in any of the preceding boxes is not sufficient.

Continuation of :

cover sheet :International Patent Classification (IPC) or both national classification and IPC

C07D 491/052 (2006.01) i

C07D 217/26 (2006.01) i

C07D 413/04 (2006.01) i

C07D 519/00 (2006.01) i

A61K 31/496 (2006.01) i

A61P 35/00 (2006.01) i

Continuation of :

Box No. V:Citations and explanations

The compound 22 disclosed in D3 (see page 454, Table 4 of D3) has fallen into the scopes of claims 1, 4, 9-10.

The compounds 14-20, 57-60, 66-67, 115, 128 disclosed in D4 (see pages 29-31, 37-38, Table 12-13 of D4) have fallen into the scopes of claims 1, 4, 9-10, and the compound 128 disclosed in D4 (see page 38 of D4) has also fallen into the scope of claim 14.

The compounds 25-30, 33, 41-43 disclosed in D5 (see page 20-21, Table 10-11 of D5) have fallen into the scopes of claims 1, 4, 9-10.

The compounds CAS no. 134538-28-6, 134538-29-7, 134538-30-0, 134538-31-1 disclosed in D6 have fallen within the scopes of claims 1-5, 9-10, 14.

Thus, claims 1-5, 9-10, 14 are not novel, and do not meet the criteria set out in PCT Article 33(2).

The compounds 37, 40, 43, 47, 49, 53-57, 59-63, 66-74 disclosed in D2 (see pages 16-23 of D2) , and the compounds 14-20, 57-60, 66-67, 115, 128 disclosed in D4 (see pages 29-31, 37-38, Table 12-13 of D4) have fallen into the scope of claim 1. D2 and D4 also disclose compositions of said compounds (see claim 4 of D2, claim 16 of D4). So the composition claimed in claim 30 is disclosed by D2 and D4. Thus, claim 30 is not novel, and does not meet the criteria set out in PCT Article 33(2).

See Supplemental Box

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of :

Box No. V:Citations and explanations

The subject matter of claims 6-8, 11-13, 15-29, 31-35 differs from D1-D6 in structure of the compounds and/or the pharmaceutical uses of the compounds. Thus the subject matter of claims 6-8, 11-13, 15-29, 31-35 is therefore new (Article 33(2) PCT).

2.3 Inventive step

The compounds or pharmaceutical compositions disclosed in D1-D6 of claims 1-5, 9-10, 14, 30 are not novel, so the compounds or pharmaceutical compositions disclosed in D1-D6 of claim 1-5, 9-10, 14, 30 could not be considered as involving an inventive step, and does not meet the criteria set out in Article 33(3) PCT.

The compounds or pharmaceutical compositions which are not disclosed in D1-D6 of claims 1-5, 9-10, 14, 30, and claims 6-8, 11-13, 15-29, 31-35 differ from D1-D6 in structure of the compounds and/or the pharmaceutical uses of the compounds.

There is no teaching in the prior arts that would prompt the skilled person in the art to use the compounds of D1-D6 as the inhibition of mutant IDH1. Therefore, it is not obvious for a person skilled in the art to obtain the compounds or pharmaceutical compositions which are not disclosed in D1-D6 of claims 1-5, 9-10, 14, 30, and claims 6-8, 11-13, 15-29, 31-35 based on D1-D6. Accordingly, the compounds or pharmaceutical compositions which are not disclosed in D1-D6 of claims 1-5, 9-10, 14, 30, and claims 6-8, 11-13, 15-29, 31-35 involve an inventive step and meet the criteria set out in Article 33(3) PCT.

2.4 Industrial applicability

The subject matter of claims 1-35 can be made or used in pharmaceutical industry and thus meets the requirements of Article 33(4) PCT.

PATENT COOPERATION TREATY

# ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

# PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

MCCARTY, Catherine, M.
Lando & Anastasi, LLP
One Main Street, Eleventh Floor
Cambridge, MA 02142
ETATS-UNIS D'AMERIQUE

| | |
|---|---|
| Date of mailing *(day/month/year)*<br>12 January 2012 (12.01.2012) | |
| Applicant's or agent's file reference<br>C2081-7019WO | IMPORTANT NOTICE |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US2010/040486 | 29 June 2010 (29.06.2010) | 29 June 2009 (29.06.2009) |

Applicant
AGIOS PHARMACEUTICALS, INC. et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Nora Lindner

e-mail: pt03.pct@wipo.int

Form PCT/IB/326 (January 2004)

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>C2081-7019WO | **FOR FURTHER ACTION** | See item 4 below |
| International application No.<br>PCT/US2010/040486 | International filing date *(day/month/year)*<br>29 June 2010 (29.06.2010) | Priority date *(day/month/year)*<br>29 June 2009 (29.06.2009) |
| International Patent Classification (8th edition unless older edition indicated)<br>See relevant information in Form PCT/ISA/237 | | |
| Applicant<br>AGIOS PHARMACEUTICALS, INC. | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

| | |
|---|---|
| | Date of issuance of this report<br>04 January 2012 (04.01.2012) |
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br>Facsimile No. +41 22 338 82 70 | Authorized officer<br>Nora Lindner<br>e-mail: pt03.pct@wipo.int |

Form PCT/IB/373 (January 2004)