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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/048,851	02/19/2016	Guoxian Wu	37JF-193349-US5	5501
117868	7590	04/18/2016	EXAMINER	
Plexxikon Inc. c/o Sheppard Mullin Richter & Hampton LLP 379 Lytton Avenue Palo Alto, CA 94301			WANG, SHENGJUN	
			ART UNIT	PAPER NUMBER
			1627	
			NOTIFICATION DATE	DELIVERY MODE
			04/18/2016	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):

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Office Action Summary	Application No. 15/048,851	Applicant(s) WU ET AL.	
	Examiner SHENGJUN WANG	Art Unit 1627	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 _____.
☐ 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) 21-33 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) 21-33 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: _____.

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

DETAILED ACTION

Claim Rejections 35 U.S.C. 112

2. The following is a quotation 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 35 U.S.C. 112 (pre-AIA), first paragraph:

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.

3. Claims 21-33 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.

4. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

5. "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc.,

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that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

6. Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents" of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

7. The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

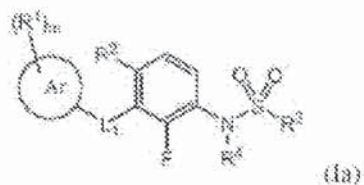
8. The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically state that for each claim drawn to a

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genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (i.e. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such comparison.

9. Scope of claims (elected invention):

A compound of formula (Ia):



or a pharmaceutically acceptable salt thereof,

wherein:

L_1 is a bond, $-N(H)C(O)-$, $-N(H)-$, $-N(H)-S(O)-$, or $-N(H)-C(NH)-$;

each R^1 is optionally substituted lower alkyl or optionally substituted heteroaryl;

R^2 is hydrogen or halogen;

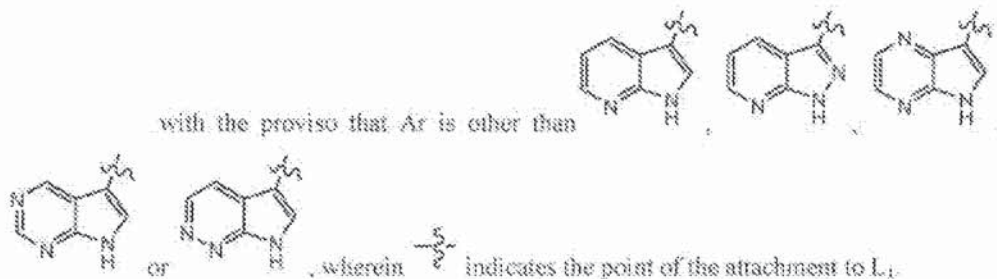
R^4 is hydrogen;

R^3 is optionally substituted lower alkyl or optionally substituted aryl;

m is 0, 1, 2, 3, 4, or 5; and

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

Ar is a monocyclic heteroaryl containing 5 to 6 atoms or a bicyclic heteroaryl containing 8 to 10 atoms wherein at least one atom is nitrogen,




Scope of disclosure

Reduction to Practice

The compounds reduced to practice support the following:

Ar is  ,  , wherein L1 is -C(O)NH-;

Ar is  , wherein L1 is -C(O)NH- or -NHC(O)-;


Reduction to structural of chemical formulas:


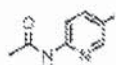
The only disclosure, is in the form of general formula with lists of possible groups. See, Formula I, paragraph [0005] and formula Ic, paragraph [0015]. This kind of disclosure is not representation of any species. A "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. MPEP 2163.1.A. and Fujikawa v. Wattanasin, 93 "3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed.Cir. 1996). Therefore, there is no species (e.g., by reduction to structural/chemical formulas) in addition to those reduced to practice.

Correlation between Structure and Function."

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10. A correlation between structure and function, for the instantly claimed genus of compounds, is neither known in the art nor disclosed in the specification. All disclosed

compounds have a linker moiety between the phenyl and the Ar. Wherein the Ar is ,

, or . The application provide no convincing evidence, or rationale that the biological activity of disclosed compounds would have been retained if the L1 and Ar in formula I vary with the scope herein defined. Thus, it is not understood what specific structures for the claimed variables will lead to compounds that have the instantly claimed activity.

III. Analysis of Fulfillment of" Written Description Requirement:

The structure/activity relationship (SAR) for binding and activity is elucidated upon analysis of IC₅₀ data of multiple compounds with various types of structural modifications. These types of studies provide insight into the structural limitations that are required for activity, i.e. specific structural elements tolerated for the claimed activity. In the absence of such correlation, it is not possible to determine what structural modifications will allow for the preservation of the desired activity.

11. In conclusion: (i) substantial structural variation exists in the genus/subgenus embraced by claims 21-33; (ii) No disclosure of species supporting the genus; (iii) common structural attributes of the claimed genus/subgenus, combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art. Thus, the specification fails to provide adequate written description for the genus of compounds claimed and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

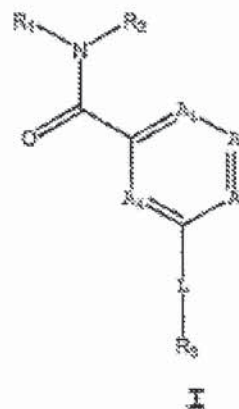
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Claim Rejections 35 U.S.C. 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. Claims 21-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dimauro et al. (WO 2007/022380, IDS).



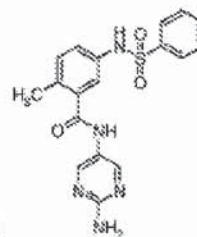
14. Dimauro et al. teach compounds having a general formula of

A^1 is CH^6 or N ;

A^2 is CH^6 or N ;

A^3 is CH^6 or N ;

wherein A^4 is CR^7 or N , R^1 is a pyridyl, or pyrimidinyl, wherein the pyridyl or pyrimidinyl may be further substituted with various substituents, L is $-NR^7S(O)_2-$; R^3 is alkyl, or aryl, see pages 26-31, and each of R^4 , R^5 , R^6 and R^7 may be hydrogen, alkyl,



or halogens. Expressly disclosed compounds include compound 93

. See, page

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114. The compounds are useful for modulating the activity of protein cytokinase and for treating cytokinase mediated disease, particularly, cancers and melanoma, such as colorectal cancer. See, particularly, the abstract, pages 7-10, 45, and the claims.

15. Dimauro et al. do not teach expressly a compound that is within the scope of claimed invention, such as wherein A4 is CR7, R4 and R7 is fluoro, or R4 is hydrogen, and wherein the R3 is pyridyl.

16. However, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to make a compound according to the general formula of Dimauro et al. wherein A4 is CR7, R7 is halogen, such as fluoro; A1 is CR4, R4 is hydrogen or halogen, and R3 is pyridyl. i.e, replace the hydrogen group in compound 93 with a fluoro; replace the methyl with hydrogen or halogen, and replace the pyrimidinyl with pyridyl, and to use the same for treatment of cytokinase mediated diseases, such as colorectal cancer.

17. A person of ordinary skill in the art would have been motivated to make a compound according to the general formula of Dimauro et al. wherein A4 is CR7, R7 is halogen, such as fluoro; A1 is CR4, R4 is hydrogen or halogen, and R3 is pyridyl. i.e, replace the hydrogen group in compound 93 with a fluoro; replace the methyl with hydrogen or halogen, and replace the pyrimidinyl with pyridyl, and to use the same for treatment of cytokinase mediated diseases, such as colorectal cancer because Dimauro et al. discloses that halogen, alkyl and hydrogen are interchangeable at the particular position, pyrimidinyl and pyridyl are also interchangeable at the particular position. One of ordinary skill in the art would have reasonably expected that such a compound be similarly active as protein cytokinase modulator.

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18. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dimauro et al. (WO 2007/022380, IDS) for reasons discussed above, and in further view of Samowitz et al.

19. Teachings of Dimauro et al. have been discussed above. Dimauro et al. do not teach expressly the treatment of cancer patients with V600E mutation.

20. However, Samowitz et al. reveals that V600E mutation are common among colorectal cancers. See, the section of introduction at page 6063.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to treat colorectal cancer patients, including those with V600E mutation.

A person of ordinary skill in the art would have been motivated to treat colorectal cancer patients, including those with V600E mutation because V600E mutation is common amount colorectal cancer and Dimauro et al. provide no teachings that the method is not suitable for colorectal cancer with V600E mutation.

Allowable Subject Matter

21. As discussed in the parent application 13/926,959, compounds as defined in claim 20 wherein L is -N(H)C(O)-, Ar is bicyclic heteroaryl as defined in the claims with the proviso provided therein, and R3 and phenyl substituted with flouro are allowable. See, the interview summary of 01/22/2016.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHENGJUN WANG whose telephone number is (571)272-0632. The examiner can normally be reached on Monday to Friday from 9:00 AM to 5:00 PM.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. 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://portal.uspto.gov/external/portal>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHENGJUN WANG/
Primary Examiner, Art Unit 1627