International Application Published Under the Patent Cooperation Treaty (PCT)

Title: COMPOSITIONS AND METHODS FOR TREATING NEOPLASIAS

Abstract: The invention provides therapeutic combinations comprising an agent that inhibits Notch signaling and an agent that inhibits B cell receptor signaling, and methods of using such agents to inhibit the survival or proliferation of a neoplastic cell.
**INTERNATIONAL SEARCH REPORT**

**International application No.**
PCT/US 17/49829

**A. CLASSIFICATION OF SUBJECT MATTER**


CPC - C 12Q 1/6868, C 12Q 260/1 06, C 12Q 260/1 56, G 01N 33/57407, G 01N 2800/52, A61K 45/06,
A61K 2300/00, C 12N 15/1 13, C 12N 231 0/14

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)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

See Search History Document

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
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<tbody>
<tr>
<td>Y</td>
<td>WO 2015/084892 A1 (UNIV CORNELL et al.) 11 June 2015 (1 1.06.2015) claims 1-1 1, 18, 21, 22, 27, 28, 31; para [00149], [00152]-[00182], [00322], [00375]</td>
<td>1-4, 7, 9, 13, (14-16)/(1-4, 7, 9), 17-19, 22, 24, 27, 28, (29-31, 33, 34)/(17-19,22,24,27,28), 32, 35-38, 40, 44-51, 53</td>
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Further documents are listed in the continuation of Box C.

* Special categories of cited documents:
  "I" 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
  "T" 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)
  "D" 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
  "N" document member of the same patent family

Date of the actual completion of the international search: 28 December 2017

Date of mailing of the international search report: 20 FEB 2018

Authorized officer: Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)
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).

This International Searching Authority found multiple inventions in this international application, as follows:

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.

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<th>Supplemental Sheet to continue</th>
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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.:
   1-4, 7, 9, 13, (14-16)/(1-4,7,9), 17-19, 22, 24, 27, 28, (29-31,33,34)/(17-19,22,24,27,28), 32, 35-38, 40, 44-51, 53, restricted to Compound E and idelasib

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.
In Continuation of Box III. Observations where unity of invention is lacking:

Group I+: claims 1-56, directed to a pharmaceutical composition comprising an inhibitor of the expression or activity of a Notch polynucleotide or polypeptide and an inhibitor of the expression or activity of a functional component of a B cell receptor polypeptide or polynucleotide, and a method of using thereof for treating leukemia or lymphoma. The composition and the method will be searched to the extent that the anti-NOTCH agent encompasses a gamma secretase inhibitor, said gamma secretase inhibitor encompasses Compound E and the anti-B cell receptor agent encompasses a PI3 kinase inhibitor, said PI3 kinase inhibitor encompasses idelisib. It is believed that claims 1-4, 7, 9, 13, (14-16)/(1-4,7,9), 17-19, 22, 24, 27, 28, (29-31,33,34)/(17-19,22,24,27,28), 32, 35-38, 40, 44-51, 53, encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass a pharmaceutical composition comprising Compound E, gamma secretase inhibitor, and idelisib, PI3 kinase inhibitor, and a method of using said composition for treating leukemia or lymphoma. Additional specific anti-Notch agent(s) and/or anti-B cell receptor agent(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected specific and-Notch agent(s) and/or anti-B cell receptor agent(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be a pharmaceutical composition comprising an anti-Notch inhibitory nucleic acid molecule and Midostaurin, the protein kinase C inhibitor, i.e., claims 1, 2, 6, 7, 11-13, (14-16)/(1-2,6,7,1), 17, 21, 26, 27, (29-31,33,34)/(17,21,26,27), 35, 44-46.

The inventions listed as Group I+ 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
The special technical feature of each invention of Group I+ is a specific anti-NOTCH agent and a specific anti-B cell receptor agent recited therein.

The special technical feature of some inventions of Group I+ is a specific gamma secretase inhibitor, or a specific anti-Notch antibody recited therein.

The special technical feature of some inventions of Group I+ is a specific BTK inhibitor or the protein kinase C inhibitor recited therein.

Common Technical Features

Some inventions of Group I+ share the technical feature of a pharmaceutical composition of claim 1. Some inventions of Group I+ share the technical feature of a method of claims 17, 28, 35, 47, or 50. However, this shared technical feature does not represent a contribution over prior art as being obvious over WO 2015/084892 A1 to UNIV CORNELL, et al., (11 June 2015) (hereinafter "Cornell") in view of a paper titled "Inhibition of NOTCH signaling by gamma secretase inhibitor engages the RB pathway and elicits cell cycle exit in T-cell acute lymphoblastic leukemia cells" by Rao, et al. (Cancer Res. 2009, 69(7):3060-3068) (hereinafter "Rao") as follows:

Cornell discloses a pharmaceutical composition comprising an effective amount of a CDK4 inhibitor and an effective amount of a BTK inhibitor (claim 1, "A pharmaceutical combination comprising: (a) a therapeutically-effective amount of Ibrutinib; (b) a therapeutically-effective amount of a CDK4 inhibitor; and (c) a pharmaceutically-acceptable excipient"; claim 5), and further discloses using said composition for treating a proliferative disorder (claim 11, "Use of a combination of (a) a therapeutically-effective amount of Ibrutinib, and (b) a therapeutically-effective amount of a CDK4 inhibitor for treating a B cell proliferative disorder in an individual in need thereof; claim 21), including those "wherein the B cell proliferative disorder is refractory to Ibrutinib or relapsed following treatment with Ibrutinib" (claims 18, 22, 31, para [00375], "Selective targeting of CDK4 with PD 0332991 resulted in prolonged early GI arrest (pGI) and a durable clinical response in recurrent MCL patients. Induction of pG1 by sustained CDK4/CDK6 inhibition was further shown to reprogram primary myeloma for bortezomib killing and primary MCL cells for PI3K inhibitor killing ex vivo. The increase in CDK4 and the maintenance of Rb expression in Ibrutinib resistance suggests that timely inhibition of CDK4 may delay or prevent the emergence or expansion of resistant MCL cells through both cell cycle control and pG1 reprogramming that lowers the threshold of Ibrutinib killing.").

Cornell does not specifically disclose an anti-NOTCH agent.

Rao discloses that "Gamma secretase inhibitors (GSI) block proteolytic activation of NOTCH receptors and may provide a targeted therapy for T-ALL... Combination treatment with GSI and a small molecule inhibitor of CDK4 produced synergistic growth inhibition, providing evidence that GSI engagement of the CDK4/RB pathway is an important mechanism of GSI action and supports further investigation of this combination for improved efficacy in treating T-ALL." (Abstract). It would have been obvious to one of ordinary skill in the art to combine, in the course of routine experimentation and with a reasonable expectation of success, Cornell and Rao, by incorporating a Gamma secretase inhibitor disclosed by Rao into the pharmaceutical composition disclosed by Cornell, to increase efficiency of the anti-cancer composition/therapy disclosed by Cornell, because Rao discloses that Gamma secretase inhibitor increases efficiency of CDK4 inhibitor (Rao, Abstract, "Combination treatment with GSI and a small molecule inhibitor of CDK4 produced synergistic growth inhibition, providing evidence that GSI engagement of the CDK4/RB pathway is an important mechanism of GSI action and supports further investigation of this combination for improved efficacy in treating T-ALL"). As said technical feature would have been obvious to one or ordinary skill in the art at the time of the invention, this cannot be considered special technical feature that would otherwise unite the inventions.

The inventions of Group I+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.