Title: INHIBITION OF TRIM62 ACTIVITY REDUCES CANCER CELL PROLIFERATION

Abstract: The present invention provides methods to treat cancers using inhibitors of the TRIM62 protein and methods to identify inhibitors and other modulators of the TRIM62 protein. Pharmaceutical compositions that contain an inhibitor of a TRIM62 protein are also provided.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
   IPC(8) - A61K 31/70; C12N 5/00 (2009.01)
   USPC - 514/44A; 435/375

   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)
   USPC - 514/44A; 435/375

   Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
   USPC - 435/6; 514/44R

   Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
   PubWEST (PGWB,USPT,USOC,EPAB,JPAB), Google Scholar: TRIM62, cancer, FLJ10759, OTTIIIUM00000004289, FLJ16558,
   DEAR1, p27, Cyclin-dependent kinase inhibitor 1B, CDKN4, KIP1
   GenCore 6.3: SEQ ID NO: 1 and 5

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>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>US 2005/0227917 A1 (WILLIAMS et al.) 13 October 2005 (13.10.2005); para [0010], [0014], [0017], [0236], [1106]; Table 148; SEQ ID NO: 22143</td>
<td>1-8, 21-28</td>
</tr>
<tr>
<td>Y</td>
<td>US 2006/0275794 A1 (CARRINO et al.) 07 December 2006 (07.12.2006); para [0045], [0049]; [0052]; SEQ ID NOs: 71912, 71913</td>
<td>1-8, 21-28</td>
</tr>
</tbody>
</table>
   <URL:http://web.archive.org/web/200710310711306/http://en.wikipedia.org/wiki/HER2/neu>; pg 1, para 1-2; pg 2, para 1, 3 | 3-6, 25-28            |

* 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
23 DEC 2009

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PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)
INTERNATIONAL SEARCH REPORT

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:

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.

Groups I-IV: claims 1-8, 21-28, drawn to a method comprising the step of administering to a human subject a therapeutically effective amount of an inhibitor of a tripartite motif-containing 62 (TRIM62) protein, wherein the TRIM62 protein has at least 95% identity to SEQ ID NO: 1, wherein claim 8 is limited to SEQ ID NO:5-8, respectively.

Group V: claims 9-14, drawn to a method of identifying a compound that inhibits proliferation of a mammalian cell, the method comprising 1) contacting a tripartite motif-containing 62 (TRIM62) protein or a host cell comprising a TRIM62 protein with a test compound; 2) assaying an activity of the TRIM62 protein or cellular expression of the TRIM62 protein in the presence of the test compound.

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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.:
   1-8, 21-28, restricted to SEQ ID NO:5

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.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)
Continuation of Box No. III: Lack of unity:

Group VI, claims 15-20, drawn to a method of diagnosing a cancer with increased levels of expression of an epidermal growth factor receptor (EGFR) receptor family member, the method comprising the steps of determining the level of expression or activity of a tripartite motif-containing 62 (TRIM62) protein in a sample from the cancer.

The inventions listed as Groups I-VI 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:

The method of screening a compound that inhibits proliferation of a mammalian cell of Group V is neither the method of using the claimed inhibitors of a tripartite motif-containing 62 (TRIM62) protein (Groups I-IV) nor the method of diagnosing a cancer with increased levels of expression of an epidermal growth factor receptor (EGFR) receptor family member (Group VI). Thus, unity of invention between Group V and Groups I-IV, VI is lacking (a priori).

The method of using the claimed inhibitors of a tripartite motif-containing 62 (TRIM62) protein (Groups I-IV) is not the method of diagnosing a cancer with increased levels of expression of an epidermal growth factor receptor (EGFR) receptor family member (Group VI). Thus, unity of invention between Groups I-IV and Group VI is lacking (a priori).

Groups I-IV share the technical feature of administering to a human subject a therapeutically effective amount of an inhibitor of a tripartite motif-containing 62 (TRIM62) protein. However, this shared technical feature is obvious over prior art. Specifically, an article entitled "TRIM E3 Ligases Interfere with Early and Late Stages of the Retroviral Life Cycle" by Uchil, et al. (PLoS Pathog Feb 2008, 4(2,e16):0001-0013) that teaches that "Silencing of endogenous human TRIM proteins was carried out using ON-TARGETplus siRNA smart pools (a mix of 4 siRNAs) from Dharmacon, Inc. pre-designed to reduce off-target effects by up to 90%. We routinely obtained 70 to 90% knock down of specific TRIM proteins as assessed by monitoring the levels of transiently expressed TRIM-GFP 36 h post-transfection. The sense sequences of siRNAs targeting ... (5) TRIM62 were #1: CUACAUGUCUGAUGCAGAUU, #2: GCGAGAAGUUCCUGGCGAUU, #3: AGACGACCGUCACAGUAUGAUU, #4: GACCAAGUCUCCACCAAGUU" (pg 3012, col 1).

In addition, no significant structural similarities can readily be ascertained among the specific recited nucleic acid sequences. As the above method of TRIM62 gene silencing was known at the time of the invention, and the claimed nucleic acid sequences do not possess significant structural similarities, the inventions of Groups I-IV do not share a special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

Groups I-VI therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.