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Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
10 May 2013

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(54) Title: COMPOSITIONS AND METHODS RELATED TO DNA DAMAGE REPAIR

(57) Abstract: The present invention provides compositions and methods for treating a cancer associated with elevated expression and/or activity of receptor typrosine kinases (e.g., Eph receptors), such as EphA5. In some embodiments, the present invention provides compositions and methods for identifying elevated expression or activity of receptor tyrosine kinases (e.g., Eph receptors), such as EphA5.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/55598

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/28; A61K 39/395 (2012.01)
USPC - 530/388.22; 424/143.1
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) - C07K 16/28; A61K 39/395 (2012.01)
USPC - 530/388.22; 424/143.1

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)
WEST; Google Scholar; PatBase; GenCore 6.3
search terms: EphA5, EPH, A5, TYRO4, HEK7, CEK7, EHK1, EHK-1, EK7, EPH homology kinase 1, ephrin, antibod$, anti, ab, extracellular, epha, epha$, 11C12

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ------ Y ------ A	US 2006/0121042 A1 (DALL'ACQUA et al.) 08 June 2006 (08.06.2006) para [0009]; [0010]; [0018]; [0026]; [0029]; [0032]; [0035]; [0037]-[0039]; [0123]; [0152]; [0198]; [0261]-[0265]; SEQ ID NO: 12.	1-4, 10-16 ---------- 5 ------ 6-9
Y	GenBank Accession P54756, Ephrin Type-A receptor 5, 27 July 2011. found online 30 January 2013 at <http://www.uniprot.org/uniprot/P54756.txt?version=126>. sequence.	5
A	WO 2011/016238 A1 (YOKOSEKI et al.) 10 February 2011 (10.02.2011) abstract; para [0012]; SEQ ID NO: 2570. This document can be viewed by entering the doc number at the following url: http://worldwide.espacenet.com/numberSearch?locale=en_EP	6-9
A	US 2005/0152903 A1 (NEWMAN et al.) 14 July 2005 (14.07.2005) para [0027]; SEQ ID NO: 9.	6-9
A	OLIVIERI et al. "Immunohistochemical Localization of EphA5 in the Adult Human Central Nervous System" J. Histochem. Cytochem.; 1999; Vol. 47, No. 7; pg. 855-861 entire document, especially pg. 856, col 1, para 6.	5

☐ 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
31 January 2013 (31.01.2013)	08 MAR 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/55598

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 extra 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.:
1-16; limited to an antibody that decreases levels of phosphorylated EphA5 in the nucleus of a cell expressing EphA5 compared to a control.

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/55598

Continuation of Box III: Lack of Unity of Invention

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+: claims 1-16, and, (in one subgroup) claims 162-169; directed to an isolated antibody, or an antigen-binding fragment thereof, characterized in that it binds to human EphA5 protein and characterized in that:
(a) it decreases levels of phosphorylated EphA5 in the nucleus of a cell expressing EphA5 as compared to a control;
(b) it decreases binding of EphA5 protein to pATM protein in a cell expressing EphA5 as compared to a control;
(c) it competes with the 11C12 antibody for binding to EphA5;
(d) it decreases cell growth, proliferation or cell survival in a cell expressing EphA5 as compared to a control; and/or
(e) any combination of (a)-(d); wherein the first invention is limited to an antibody that decreases levels of phosphorylated EphA5 in the nucleus of a cell expressing EphA5 as compared to a control (claims 1-16)(applicants may opt for additional antibodies to be searched by specifying the antibody characteristic, and paying an additional invention search fee for each elected antibody. Claims 162-169 are included in the invention directed to an antibody that competes with 11C12 antibody for binding to EphA5, and will be searched if payment for said search is made).

Group II: claim 17, directed to a method of producing an isolated antibody, or an antigen-binding fragment thereof, characterized in that it competes with an EphA5 ligand for binding to EphA5 comprising: providing a cell expressing the isolated antibody; and culturing the cell under conditions permissive for expression of the antibody thereby producing the antibody.

Group III: claims 18-38, directed to a pharmaceutical composition for treating a cell hyperproliferative disorder associated with elevated levels of EphA5, comprising a therapeutically effective amount of an agent that reduces the expression of the EphA5, reduces EphA5 phosphorylation or reduces the level of EphA5 in the nucleus of EphA5 expressing cells.

Group IV: claims 39-111, directed to a method of treating a cell hyperproliferative disorder, potentially also express elevated levels of EphA5 or have an elevated EphA5 activity, comprising administering a therapeutically effective amount of an agent that reduces the expression of the EphA5, reduces EphA5 phosphorylation, or reduces the level of EphA5 in nucleus of EphA5 expressing cells.

Group V: claims 112-145, directed to a method of treating a patient having a cell hyperproliferative disorder, the method comprising administering in combination an agent that reduces expression or activity of EphA5 and a DNA damaging agent.

Group VI: claims 146-160, directed to a method of identifying a patient likely to benefit from therapy, the method comprising steps of:
obtaining an expression or activity level of EphA5 from a patient sample; and
determining that the level of EphA5 expression or activity is elevated as compared to a control level.

Group VII: claim 161, directed to a method of identifying agents that regulate phosphorylation of EphA5 comprising:
providing a collection of one or more test agents;
contacting the one or more test agents with a system comprising EphA5, or a portion thereof; and
comparing the phosphorylation of EphA5 in the presence and absence of the one or more test agents.

Group VIII: claims 170-172, directed to a method for sensitizing cells to DNA damaging agents or reversing resistance to DNA damaging agents comprising contacting the cell with an agent that reduces EphA5 expression or activity.

The inventions listed as Groups I+ and II-VIII 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 special technical features of the claims of Groups I+ and II-VIII are disclosed in the Group descriptions, above.

- Please see next extra sheet for continuation -

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/55598

Continuation of First Extra Sheet: Lack of Unity of Invention

The only common technical element shared by the above groups is that they are related to agents which reduce EphA5 activity or expression. The claims of Groups I+ and II share the common technical element of being directed to antibodies that bind to a human EhpA5 protein. The claims of Groups III-V share the common technical element of being related to treatment of a hyperproliferative disorder associated with elevated levels of EphA5 comprising an agent that reduces EphA5 activity, phosphorylation or expression. Groups III-VI share the common technical element of being related to EphA5 expression or activity. Groups V and VIII share the common technical element of a DNA-damaging agent. Groups VI and VII share the common technical element of being related to methods of identification associated with EphA5. These common technical elements do not represent an improvement over the prior art of US 2006/0121042 A1 to Dall'Acqua et al., which teaches a method of treating patient having a cell hyperproliferative disorder (para [0305]) wherein the cells associated with said disorder were previously determined to express elevated levels of EphA5 (overexpressed; para [0007]) or have an elevated EphA5 activity (para [0130]), or phosphorylation (para [0130]) the method comprising administering an agent that reduces the level or activity of EphA5 (para [0007]-[0009] and [0305]; it should be noted that, although Dall'Acqua does not specifically recite elevated levels of EphA5 in comparison to a control, the term overexpression, as used by Dall'Acqua, inherently includes comparison to a control as a means of determining "overexpression"). Dall'Acqua further discloses wherein the agent may comprise an antibody (para [0010]) that binds to EphA5 (para [0009]), and wherein the antibody may compete with or reduce binding of the natural ligand for the receptor (para [0010], [0118]). Additionally Dall'Acqua teaches agents which regulate or modulate the phosphorylation (para [0010]) of EphA5 (para [0009]). also, Dall'Acqua teaches the use of DNA-damaging agents, such as alkylating agents (para [0213]). Although Dall'Acqua teaches wherein these agents may be conjugated to the antibodies rather than provided in combination therewith, it would have been obvious to a person of ordinary skill in the art to have provided said agents in combination with an antibody as taught by Dall'Acqua in order to treat proliferative diseases, such as cancer, because said agents were well known in the art to be used as cancer chemotherapeutics, even in the absence of an adjunct therapy, such as administering antibodies, as taught by Dall'Acqua. Furthermore, although Dall'Acqua does not specifically recite an antibody which competes with 11C12, applicants indicate wherein said antibody binds to residues 1-72 of a fragment corresponding to amino acids 304-467 of the human EphA5 protein (para [0032], instant specification), this region corresponds to amino acids 357-459 of the full-length polypeptide. This corresponds to the C-terminal portion of the cysteine-rich region of the polypeptide, and the n-terminal portion of the first fibronectin-III domain (see GenBank Accession P54756). Dall'Acqua teaches wherein the antibodies may specifically bind to the Eph5A receptor, or a fragment thereof (para [0026]), wherein said fragments may include the first fibronectin-III domain (para [0261]). Thus it would have been obvious to a person of ordinary skill in the art to have produced antibodies according to the teaching of Dall'Acqua which would have competed with the 11C12 antibody. Dall'Acqua finally also teaches methods of identifying agents which relate to EphA5 activity (para [0105]).

Therefore, the inventions of Groups I+ and II-VIII lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.