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- with international search report (Art. 21(3))
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(54) Title: IDENTIFICATION OF MHC CLASS I PHOSPHO-PEPTIDE ANTIGENS FROM BREAST CANCER UTILIZING SHLA TECHNOLOGY AND COMPLEMENTARY ENRICHMENT STRATEGIES

(57) Abstract: The present invention describes novel tumor-specific phosphorylated peptides, nucleic acids encoding those peptides, and antibodies generated against said peptides. The genes, peptides, and antibodies described herein may be used as diagnostic indicators of the presence of breast cancer and/or used in therapeutics to treat breast cancer.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 13/42908

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/00; C12N 5/07; A61K 38/08; C07K 16/00 (2013.01)

USPC - 424/184.1, 435/344, 514/21.6, 530/387.9

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- 424/184.1, 435/344, 514/21.6, 530/387.9

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/19.3, 435/325, 530/389.1, 530/327Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(PGPB,USPT,USOC,EPAB,JPAB); Google Patents; Google Scholar: Human cullin 4A, CUL4A, amino acids 5-15, tumor antigen, APRKGSFALM, phosphorylated epitope, phosphopeptide antigen, serine, phosphorylated serine, Ser10
GenCore 6.4.1: SEQ ID NO:70

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/134883 A1 (ZHOU, et al.) 05 November 2009 (05.11.2009) claims 11, 12; SEQ ID NO:18, amino acids 5-15	1, 10, 12-14, 17, 19, 20
A	Hojlund, et al. In vivo phosphoproteome of human skeletal muscle revealed by phosphopeptide enrichment and HPLC-ESI-MS/MS. J Proteome Res. 2009, 8(11):4954-4965; Abstract, pg 18 [of the posted document], 15th line from the bottom	1, 10, 12-14, 17, 19, 20
A	Cell Signaling Technology, Inc. CUL4A Antibody. 16 September 2010. [Retrieved from the Internet 14 January 2014: <http://www.cellsignal.com/pdf/2699.pdf>]; col 1	1, 10, 12-14, 17, 19, 20
A	Liu, et al. CUL4A abrogation augments DNA damage response and protection against skin carcinogenesis. Mol Cell 2009, 34(4):451-60; Abstract	1, 10, 12-14, 17, 19, 20
A	Ren, et al. Oncogenic CUL4A determines the response to thalidomide treatment in prostate cancer. J Mol Med (Berl) ePub 16 March 2012, 90(10):1121-32; Abstract	1, 10, 12-14, 17, 19, 20
A	Hung, et al. Cul4A is an oncogene in malignant pleural mesothelioma. J Cell Mol Med. 2011, 15(2):350-8; Abstract	1, 10, 12-14, 17, 19, 20
A	Lee, et al. Pathogenic Role of the CRL4 Ubiquitin Ligase in Human Disease. Front Oncol. 06 March 2012, 2:21; Abstract	1, 10, 12-14, 17, 19, 20
A	Jia, et al. SCF E3 ubiquitin ligases as anticancer targets. Curr Cancer Drug Targets 2011, 11(3):347-56; Abstract	1, 10, 12-14, 17, 19, 20
A	WO 2011/149909 A2 (HUNT, et al.) 01 December 2011 (01.12.2011) Abstract, Table 2A-2F	1, 10, 12-14, 17, 19, 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

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13 January 2014 (13.01.2014)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 13/42908

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Zarling, et al. MHC-restricted phosphopeptides as broad-based immunotherapeutic targets for cancer. Poster Presentations - Tumor Vaccine Development. Proceedings: AACR 103rd Annual Meeting 2012-- Mar 31-Apr 4, 2012; Chicago, IL. Cancer Research 15 April 2012, Volume 72, Issue 8, Supplement 1, Abstract 1584; in entirety	1, 10, 12-14, 17, 19, 20
A	Zarling, et al. Identification of class I MHC associated phosphopeptides as targets for cancer immunotherapy. Proc Natl Acad Sci USA 2006, 103(40):14889-94	1, 10, 12-14, 17, 19, 20
A	US 2012/0129776 A1 (Cohen, et al.) 24 May 2012 (24.05.2012) para [0200], [0263], [0272] [0660] [0704]	1, 10, 12-14, 17, 19, 20
A	US 2012/0021432 A1 (Yu, et al.) 26 January 2012 (26.01.2012) para [0198], [0199], claims 4-8	1, 10, 12-14, 17, 19, 20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 13/42908

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.

Group I+: claims 1-20, drawn to an isolated 9 to 20 amino acid long phosphopeptide comprising a specified amino acid sequence, a composition comprising said phosphopeptide, an antibody specifically binding to said phosphopeptide, and a method of administering said phosphopeptide to a patient to treat breast cancer. Group I+ will be searched to the extent that it reads on an isolated phosphopeptide of SEQ ID NO: 70, without fee. It is believed that claims 1, 4-7, 9, 10, 12-17, 19, 20 read on this first named invention. Applicants must indicate, if applicable, the claims which read on 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/examined. An exemplary election would be: an isolated phosphopeptide of SEQ ID NO:84, i.e. claims 1-20.

[NOTE: Claims 4-7, 9, 15, 16, were excluded from the search, because they are drawn to a non-elected subject matter.]
***** See Supplemental Sheet to continue *****

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, 10, 12-14, 17, 19, 20, restricted to SEQ ID NO: 70

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:

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 phosphopeptide of a specific amino acid sequence. The inventions do not share the special technical feature, because no significant structural similarities can readily be ascertained among the phosphopeptides.

Common Technical Features

The inventions of Group I+ share the technical feature of an isolated phosphopeptide. However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2012/0021432 A1 to Yu, et al. (26 January 2012) (hereinafter "Yu") that discloses an isolated phosphopeptide (claim 4, "[a]n isolated peptide comprising the amino acid sequence of SEQ ID NO: 1 phosphorylated at one or more serine, threonine, or tyrosine residues"). As said technical feature was known in the art at the time of the invention, this cannot be considered special technical feature that would otherwise unify the inventions of Group I+.

The inventions of Group I+ also share the technical feature of an antibody that specifically binds to a phosphopeptide. However, this shared technical feature does not represent a contribution over prior art as being anticipated by Yu, as above, that discloses an antibody that specifically binds to a phosphopeptide (claim 2, "... the antibody specifically binds the protein of SEQ ID NO: 1 phosphorylated at one or more threonine residues"). As said technical feature was known in the art at the time of the invention, this cannot be considered special technical feature that would otherwise unify the inventions of Group I+.

Finally, the inventions of Group I+ also share the technical feature of method of treating or preventing breast cancer comprising administering to a patient in need thereof a composition comprising an isolated phosphopeptide of a specified amino acid sequence in combination with a pharmaceutically acceptable carrier. However, this shared technical feature does not represent a contribution over prior art as being obvious over a paper titled "Inhibition of BRCT(BRCA1)-phosphoprotein interaction enhances the cytotoxic effect of Olaparib in breast cancer cells: A proof of concept study for synthetic lethal therapeutic option" by Pessetto, et al. (Breast Cancer Res Treat. ePub 06 May 2012, 134(2): 511-517) (hereinafter "Pessetto") in view of US 2011/0104713 A1 to Yaffe, et al. (05 May 2011) (hereinafter "Yaffe") as follows:

Pessetto discloses that treating HeLa and MDA-MB-231 cell lines with a composition comprising an isolated phosphopeptide (Abstract, pg 3 of the posted document, para 3, BRCA1 inhibitor peptide 2, (Ac-R10G-pSPTF-CO₂H)) in combination with Olaparib, the inhibitor of poly(adenosine diphosphate [ADP]-ribose) polymerase (Abstract) "sensitizes HeLa and MDA-MB-231 cells... to Olaparib mediated growth inhibition and apoptosis" (Abstract).

Pessetto specifically discloses neither administering said composition to a breast cancer patient nor that said composition comprises a pharmaceutically acceptable carrier.

Yaffe discloses "a pharmaceutical composition containing (i) a phosphopeptide containing a pSer or pThr and (ii) a pharmaceutically acceptable carrier, where the phosphopeptide is present in amounts that, when administered to a subject, ameliorates a neoplastic disease" (para [0045]).

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, Pessetto with Yaffe by administering to a breast cancer patient a composition comprising an isolated phosphopeptide of a specified amino acid sequence disclosed by Pessetto (Abstract, pg 3 of the posted document, para 3, BRCA1 inhibitor peptide 2, (Ac-R10G-pSPTF-CO₂H)), in combination with a pharmaceutically acceptable carrier disclosed by Yaffe, because Pessetto further discloses that "inhibition of BRCA1 by [phosphopeptide] 2... provide[s] the basis for developing high affinity BRCT(BRCA1) inhibitors as adjuvants to treat sporadic breast and ovarian cancers" (Abstract).

In addition, WO 2009/134883-A1 (Zhou) discloses an amino acid sequence which is at least 90% identical to the claimed SEQ ID NO: 70 (SEQ ID NO 18, amino acids 5-15, 90.9% identity, one mismatch at the position 15).

As said common technical feature would have been obvious to one of ordinary skill in the art at the time of the invention, this cannot be considered common technical feature that would otherwise unify the inventions of Group I+.

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