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(71) Applicant (for all designated States except US): **OK-**

LAHOMA MEDICAL RESEARCH FOUNDATION
[US/US]; 825 Ne 13th Street, Ms 52, Oklahoma City, OK
73104 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DONG, Yunzhou**

[US/US]; Oklahoma Medical Research Foundation, 825
NE 13th Street, Ms 52, Oklahoma City, OK 73104 (US).
CHEN, Hong [—/US]; Oklahoma Medical Research
Foundation, 825 NE 13th Street, Ms 52, Oklahoma City,
OK 73104 (US).

(74) Agent: **HIGHLANDER, Steven, L.**; **FULBRIGHT & JA-**

WORSKI L.L.P., 98 San Jacinto Boulevard, Suite 1100,
Austin, TX 78701 (US).

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24 April 2014

(54) Title: UBIQUITIN INTERACTING MOTIF PEPTIDES AS CANCER THERAPEUTICS

(57) Abstract: The disclosure involves the use peptides comprising ubiquitin interacting motifs (UIMs) alone or in combination with other agents to treat diseases involving neovascularization, such as cancer. Further disclosed are UIM-containing peptide sequences and cancers that can be treated using the peptides comprising UIMs. The routes for administration of the peptides comprising UIMs are also described.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/23286

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/10; A61K 38/16; A61K 38/00 (2012.01)

USPC - 514/21.4; 514/21.3; 514/1.1, 514/19.3

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) - A61K 38/10; A61K 38/16; A61K 38/00 (2012.01)

USPC - 514/21.4; 514/21.3; 514/1.1, 514/19.3; 530/324, 530/325, 530/326

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

IPC(8) - A61K 38/10; A61K 38/16; A61K 38/00 (2012.01) - see keyword below

USPC - 514/21.4; 514/21.3; 514/1.1, 514/19.3; 530/324, 530/325, 530/326 - see keyword below

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

PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google: UIM domain, ubiquitin interacting motif, interactive, treating, cancer, malignant, neoplasm, recurrent, metastatic, multidrug resistant, DNA repair, administer, intra-tumoral, regional, local, systemic, oral, intravenous, intraarterial, brain, head and neck, throat, esophageal, nasopharyngeal, lung, s

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FISHER et al. Structure and Ubiquitin Binding of the Ubiquitin-interacting Motif. J Biol Chem. 2003, Vol. 278(31), p. 28976-84. Abstract; pg 28976, col 1, and col 2, para 2; and pg 28978, Table II	1-7
Y	US 2007/0196897 A1 (FEDER et al.) 23 August 2007 (23.08.2007), para [0081], [0113], [0205], [0544], [0649], [0754], [0797], [0826], [0846], [0847], [0870], [0871], [0964], and [1287]	1-7
A	YAN et al. The ubiquitin-interacting motif containing protein RAP80 interacts with BRCA1 and functions in DNA damage repair response. Cancer Res. 2007, Vol. 67(14), p. 6647-56. Abstract; and pg 6647, col 2, para 2	1-7
A	WO 2010/028058 A1 (TOWNER et al.) 11 March 2010 (11.03.2010), Abstract; and pg 1, ln 17-18	1-7
A	US 2010/0021941 A1 (MARBLESTONE et al.) 28 January 2010 (28.01.2010), para [0007], [0008], and [0086]	1-7
A	US 2006/0286574 A1 (ROMESBERG et al.) 21 December 2006 (21.12.2006), para [0009], [0027], [0182], [0261], and [0289]	1-7
A	LI et al. Mdm2 Directs the Ubiquitination of beta-Arrestin-sequestered cAMP Phosphodiesterase-4D5. J Biol Chem. 2009, Vol. 284(24), p. 16170-82. Abstract; pg 16171, col 2, last para; pg 16172, Table 1; and pg 16174, Fig 3	1-7
A	US 2004/0171085 A1 (Joazeiro) 02 September 2004 (02.09.2004), Abstract, para [0006], [0011]	1-7

☐ 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

10 July 2012 (10.07.2012)

Date of mailing of the international search report

03 AUG 2012

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/23286

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.

Group I+: claims 1-10, drawn to a method of treating cancer in a subject comprising administering to said subject an ubiquitin interactive motif (UIM)-containing peptide. The first named invention (claims 1-7) is limited to administering to said subject an ubiquitin interactive motif (UIM)-containing peptide. Applicant is invited to elect the method further comprising a secondary anti-cancer therapy (claims 8-10), including wherein the secondary anti-cancer therapy is 2,4-disulfonyl phenyl tert-butyl nitron (2,4-ds-PBN), to be searched by paying additional fee for the search.

Group II, claims 11-20, drawn to a method of inducing non-productive vessel formation in a subject comprising administering to said subject an ubiquitin interactive motif (UIM)-containing peptide, and the method further comprising a secondary treatment, wherein the secondary treatment is ruboxistaurine, VEGF IL-20, ranibizumab, bevacizumab or pegaptanib, to be searched by paying additional fee for the search. *****Continued in the 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.:
1-7, limited to administering to said subject an ubiquitin interactive motif (UIM)-containing peptide.

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 12/23286

Continuation of:
Box No III (unity of invention is lacking)

Group III, claims 21-25, drawn to a pharmaceutical composition comprising a ubiquitin interactive motif (UIM)-containing peptide dispersed in a pharmalogically acceptable medium, carrier or diluent.

The inventions listed as Groups I+-III 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:

Groups I+- II do not include the inventive concept of a pharmaceutical composition comprising a ubiquitin interactive motif (UIM)-containing peptide dispersed in a pharmalogically acceptable medium, carrier or diluent, as required by Group III.

Group I+ and III do not include the inventive concept of inducing non-productive vessel formation in a subject, as required by Group II.

Groups II and III do not include the inventive concept of treating cancer in a subject, as required by Groups I+.

Furthermore, among Groups I+ or/ and II, each secondary therapy requires therapeutic agents that are structurally and functionally different from an ubiquitin interactive motif (UIM)-containing peptide in each Group I+ or Group II; and the methods or agents for a secondary therapy in Group I+ each is completely different from each of the agents for a secondary therapy in Group II.

The inventions of Groups I+ through III share the technical feature of an ubiquitin interactive motif (UIM)-containing peptide, and Group I+ and Group II further share the technical feature of administering to said subject an ubiquitin interactive motif (UIM)-containing peptide. However, this shared technical feature does not represent a contribution over prior art. Specifically, Claim 1 lacks an inventive step under PCT Article 33(3) as being obvious over an article entitled 'Structure and Ubiquitin Binding of the Ubiquitin-interacting Motif' by FISHER et al. (hereinafter 'Fisher'; J Biol Chem. 2003, Vol. 278(31), p. 28976-84), in view of US 2007/0196897 A1 to FEDER et al. (hereinafter 'Feder') as follows:

Fisher discloses an ubiquitin interactive motif (UIM)-containing peptide (Abstract - 'the ubiquitin-interacting motif (UIM) ...UIM peptides'; pg 28978, Table II). Fisher further discloses wherein ubiquitin interactive motif (UIM)-containing peptide plays an important role in DNA repair (pg 28976, col 1 - 'protein ubiquitylation also plays important roles in a large number of other biological processes, including DNA repair'; Abstract - 'Ubiquitylation is used to target proteins into a large number of different biological processes ... Ubiquitylated proteins are typically recognized using one of several different conserved ubiquitin binding modules.... the ubiquitin-interacting motif (UIM)'; Please also see Yan et al.: pg 6647, col 2, para 2 - 'ubiquitin-interacting motifs (UIM)...UIMs have been found in a variety of proteins with roles...DNA repair').

Fisher does not specifically teach a method of treating cancer in a subject comprising administering to said subject an ubiquitin interactive motif (UIM)-containing peptide. Feder discloses a method for treating cancer in a subject comprising administering to said subject a peptide (para [0081] - 'treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide'; para [0113] - 'treating, or ameliorating a medical condition with the polypeptide ... wherein the medical condition is a cancer'; para [0544] - a polypeptide of the invention can be administered to various host') --- wherein the peptide plays a role in DNA repair (para [0205] - 'polypeptides, ... are useful for treating, ...or ameliorating DNA-repair deficiencies, particularly ... skin cancer...or cancers';para [0754] - 'polypeptides of the present invention can be used to treat, ... patients can be administered a polypeptide ...to supplement absent or decreased levels of a different polypeptide ... DNA repair proteins').

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Fisher and Feder, to obtain an ubiquitin interactive motif (UIM)-containing peptide, as taught by Fisher, and further wherein the peptide is used in a method of treating cancer in a subject comprising administering to said subject an ubiquitin interactive motif (UIM)-containing peptide, based on the combination of Feder and Fisher, in order to use different peptides that play an important role in DNA repair for facilitating treating different cancers with desired effect. Without a shared special technical feature, the inventions lack unity with one another.

The inventions of Groups I+ and Group II further share the technical feature of a secondary therapy. However, this shared technical feature does not represent a contribution over prior art. Specifically, Feder further discloses a method for treating cancer in a subject comprising a secondary therapy (para [0623] - 'the invention may be administered alone or in combination with other types of treatments ... radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents'; para [0081], [0113]). Furthermore, WO 2010/028058 A1 to TOWNER et al. discloses a method of using 2,4-disulfonyl phenyl tert-butyl nitron (2,4-ds-PBN) as an agent in a combination therapy for treating cancer (Abstract - 'the use of 2,4-disulfonyl phenyl tert-butyl nitron (2,4-ds-PBN), alone or in combination with chemo- or radiotherapy, to treat gliomas'; pg 1, ln 17-18 - 'Gliomas are a diverse group of brain tumors that arise from normal "glial" cells of the brain'). Without a shared special technical feature, the inventions lack unity with one another.

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