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13 March 2014

(54) Title: MELANOSOME TRANSPORT INHIBITION FOR THE TREATMENT OF MELANOMA

(57) Abstract: This invention relates to methods of increased the sensitivity of cancers, such as melanoma, to cytotoxic anti-cancer compounds, such as methotrexate, by inhibiting melanosome trafficking in the cancer cells, for example using Akt2 signalling inhibitors, such as 7-hydroxystraurosporine. Methods of treatment and compounds for use therein are provided.



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/064944

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/519 A61K31/553 G01N33/48
ADD.

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)
A61K G01N

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)

EPO-Internal, BIOSIS, EMBASE, FSTA, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	P. N. LARA ET AL: "The Cyclin-Dependent Kinase Inhibitor UCN-01 Plus Cisplatin in Advanced Solid Tumors: A California Cancer Consortium Phase I Pharmacokinetic and Molecular Correlative Trial", CLINICAL CANCER RESEARCH, vol. 11, no. 12, 15 June 2005 (2005-06-15), pages 4444-4450, XP055082170, ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-04-2602 abstract page 4447; table 2 page 4447, left-hand column, last paragraph page 4449, right-hand column, last paragraph ----- -/--	1-15,17, 19,22,24



Further documents are listed in the continuation of Box C.



See patent family annex.

* 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

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/064944

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TOBIAS SINNBERG ET AL: "Inhibition of PI3K-AKT-mTOR Signaling Sensitizes Melanoma Cells to Cisplatin and Temozolomide", JOURNAL OF INVESTIGATIVE DERMATOLOGY, vol. 129, no. 6, 11 December 2008 (2008-12-11), pages 1500-1515, XP055082400, ISSN: 0022-202X, DOI: 10.1038/jid.2008.379 abstract page 1501, left-hand column, last paragraph - page 1510 page 1500, left-hand column -----	1-11,14, 15,17, 19,22-24
X	MADHUNAPANTULA S V ET AL: "The Akt signaling pathway: An emerging therapeutic target in malignant melanoma", CANCER BIOLOGY & THERAPY, LANDES BIOSCIENCE, vol. 12, no. 12, 15 December 2011 (2011-12-15), pages 1032-1048, XP009160783, ISSN: 1538-4047, DOI: 10.4161/CBT.12.12.18442 page 1037, right-hand column, last paragraph - page 1038, left-hand column, paragraph 1 page 1039 - page 1041 page 1041, left-hand column, paragraph 3 -----	1-12,14, 15,17, 19,22-25
X	R. P. PEREZ ET AL: "Modulation of Cell Cycle Progression in Human Tumors: A Pharmacokinetic and Tumor Molecular Pharmacodynamic Study of Cisplatin Plus the Chk1 Inhibitor UCN-01 (NSC 638850)", CLINICAL CANCER RESEARCH, vol. 12, no. 23, 1 December 2006 (2006-12-01), pages 7079-7085, XP055082356, ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-06-0197 the whole document ----- -/--	1-15,17, 19,22,24

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/064944

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHI H ET AL: "Combinatorial Treatments that Overcome PDGFR driven resistance of melanoma cells to V600EB RAF Inhibition", CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 71, no. 15, 1 August 2011 (2011-08-01), pages 5067-5074, XP002697373, ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-11-0140 abstract page 5070, right-hand column, last paragraph - page 5071, right-hand column, paragraph 1 page 5073, left-hand column, last paragraph - right-hand column, paragraph 1 -----	1-12,14, 15,22, 24-27
X	F. MEIER ET AL: "Combined targeting of MAPK and AKT signalling pathways is a promising strategy for melanoma treatment", BRITISH JOURNAL OF DERMATOLOGY, vol. 156, no. 6, 1 June 2007 (2007-06-01), pages 1204-1213, XP055082399, ISSN: 0007-0963, DOI: 10.1111/j.1365-2133.2007.07821.x abstract page 1210, right-hand column - page 1212 -----	1-12,14, 15,22,24
X	R. POLAK ET AL: "The PI3K/PKB signaling module as key regulator of hematopoiesis: implications for therapeutic strategies in leukemia", BLOOD, vol. 119, no. 4, 26 January 2012 (2012-01-26), pages 911-923, XP055082549, ISSN: 0006-4971, DOI: 10.1182/blood-2011-07-366203 table 2 -----	8-15,17, 18,20, 21,23
X,P	Maria Piedad Fernández-Pérez ET AL: "Suppression of Antifolate Resistance by Targeting the Myosin Va Trafficking Pathway in Melanoma", Neoplasia, 1 July 2013 (2013-07-01), pages 826-839, XP055082147, DOI: 10.1593/neo.13320 Retrieved from the Internet: URL:http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3689245/pdf/neo1507_0826.pdf [retrieved on 2013-10-02] abstract page 832, right-hand column, last paragraph - page 838, left-hand column -----	1-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2013/064944

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:

see additional 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 an 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.:

1-27

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-27

A method of treatment of melanoma comprising administering a cytotoxic anti-cancer compound and a melanosome transport inhibitor to an individual in need thereof.

A pharmaceutical formulation comprising an melanosome transport inhibitor and a cytotoxic anti-cancer compound, optionally for use in the treatment of melanoma.

2. claims: 28-34

A method of screening for a compound with activity in increasing the sensitivity of a melanoma cell to a cytotoxic anti-cancer compound comprising;

contacting a cancer cell with a cytotoxic anti-cancer compound and determining the activation of MyoVa in the melanoma cell,

wherein a decrease in activation of MyoVa in the presence relative to the absence of test compound is indicative that the compound is active in increasing the sensitivity of a melanoma cell to the cytotoxic anti-cancer compound.

3. claims: 35-40

A method of treatment of a melanoma comprising administering a cytotoxic anti-cancer compound to an individual in need thereof, wherein the melanoma is characterised by the absence of expression of MyoVa isoforms comprising SEQ ID NO:1.

A cytotoxic anti-cancer compound for use in the treatment of melanoma in an individual, wherein the melanoma is characterised by the absence of expression of MyoVa isoforms comprising SEQ ID NO: 1.

Use of a cytotoxic anti-cancer compound in the manufacture of a medicament for use in the treatment of melanoma characterised by the absence of expression of MyoVa isoforms comprising SEQ ID NO: 1.

4. claims: 41, 42

A method of selecting a treatment for an individual with melanoma, comprising providing a sample of one or more melanoma cells obtained from the individual, and determining the presence of expression of one or more MyoVa isoforms comprising SEQ ID NO:1 in the cells; or determining the absence of expression of MyoVa isoforms comprising SEQ ID NO:1 in the cells, and;

selecting treatment with an cytotoxic anti-cancer compound in combination with a melanosome transport inhibitor if

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

expression is present, or selecting treatment with an
cytotoxic anti-cancer compound if expression is absent.
