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(72) Inventors; and

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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))

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5 November 2009

(54) Title: METHODS FOR THE IDENTIFICATION OF AGENTS THAT INHIBIT MESENCHYMAL -LIKE TUMOR CELLS OR THEIR FORMATION

(57) Abstract: The present invention provides tumor cell preparations for use as models of the EMT process for use in the identification of anti-cancer agents, wherein said tumor cell preparations comprise cells of the epithelial tumor cell line H358, which are stimulated by receptor ligands to induce EMT, or which have been engineered to inducibly express a protein that stimulates EMT. The present invention also provides methods of identifying potential anti-cancer agents by using such tumor cell preparations to identify agents that inhibit EMT, stimulate MET, or inhibit the growth of mesenchymal-like cells. Such agents should be particularly useful when used in conjunction with other anti-cancer drugs such as EGFR and IGF-1R kinase inhibitors, which appear to be less effective at inhibiting tumor cells that have undergone an EMT.



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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/001456

A. CLASSIFICATION OF SUBJECT MATTER INV. G01N33/574				
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) 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 practical, search terms used) EPO-Internal, EMBASE, BIOSIS, INSPEC, WPI Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	SHINTANI Y ET AL: "Collagen I promotes epithelial-to-mesenchymal transition in lung cancer cells via transforming growth factor-[beta] signaling" AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY 200801 US, vol. 38, no. 1, January 2008 (2008-01), pages 95-104, XP002535366 ISSN: 1044-1549	1-12,91		
A	the whole document In particular: Title, Abstract and Materials and methods; p. 96, col. 1, l. 20-28; p. 98, col. 2, l. 3 - p. 99, l. 2; p. 100-103, discussion. ----- -/--	45-60, 83-90		
<table style="width:100%; border:none;"> <tr> <td style="width:50%; border:none;"><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.</td> <td style="width:50%; border:none;"><input checked="" type="checkbox"/> See patent family annex.</td> </tr> </table>			<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.
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* 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 document 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 <p align="center">4 September 2009</p>	Date of mailing of the international search report <p align="center">16/09/2009</p>			
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer <p align="center">C.F. Angioni</p>			

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/001456

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHAABAN SALAM ET AL: "Role of PAK1 and PAK2 kinases in Snail phosphorylation and in the epithelial-mesenchymal transition." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 48, April 2007 (2007-04), page 247, XP002535367	1-12,91
A	& 98TH ANNUAL MEETING OF THE AMERICAN-ASSOCIATION-FOR-CANCER-RESEARCH; LOS ANGELES, CA, USA; APRIL 14 -18, 2007 ISSN: 0197-016X the whole document	45-60, 83-90
Y	----- US 2007/212738 A1 (HALEY JOHN D [US] ET AL) 13 September 2007 (2007-09-13)	1-12,91
A	the whole document In particular: paragraphs 13, 15-22, 30, 37, 38, 164-167, 237-265.	45-60, 83-90
Y	----- US 2006/211060 A1 (HALEY JOHN D [US] ET AL) 21 September 2006 (2006-09-21)	1-12,91
A	the whole document In particular: paragraphs 13, 15-22, 36, 49, 50, 58, 59, 147-150, 238-243.	45-60, 83-90
Y	----- SOKOL JONATHAN P ET AL: "The use of cystatin C to inhibit epithelial-mesenchymal transition and morphological transformation stimulated by transforming growth factor-beta." BREAST CANCER RESEARCH : BCR 2005, vol. 7, no. 5, 2005, pages R844-R853, XP002535368 ISSN: 1465-542X	1-12,91
A	the whole document In particular: Title and Abstract; Fig. 1-6.	45-60, 83-90
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/001456

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>AYSE Y DEMIR ET AL: "Molecular characterization of soluble factors from human menstrual effluent that induce epithelial to mesenchymal transitions in mesothelial cells" CELL AND TISSUE RESEARCH, SPRINGER, BERLIN, DE, vol. 322, no. 2, 1 November 2005 (2005-11-01), pages 299-311, XP019346603 ISSN: 1432-0878</p>	1-12,91
A	<p>the whole document</p> <p>In particular: Title, Abstract and Materials and methods.</p>	45-60, 83-90
A	<p>AYRAULT O ET AL: "Involvement of the transcriptional factor E2F1 in the regulation of the rRNA promoter" EXPERIMENTAL CELL RESEARCH, ACADEMIC PRESS, US, vol. 312, no. 7, 15 April 2006 (2006-04-15), pages 1185-1193, XP024945011 ISSN: 0014-4827 [retrieved on 2006-04-15] the whole document</p>	1-12, 45-60, 83-91
A	<p>BARTLING B ET AL: "Down-regulation of the receptor for advanced glycation end-products (RAGE) supports non-small cell lung carcinoma" CARCINOGENESIS 200502 GB, vol. 26, no. 2, February 2005 (2005-02), pages 293-301, XP002544326 ISSN: 0143-3334 the whole document</p>	1-12, 45-60, 83-91
A	<p>BARTLING B ET AL: "Proliferative stimulus of lung fibroblasts on lung cancer cells is impaired by the receptor for advanced glycation end-products" AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY 200601 US, vol. 34, no. 1, January 2006 (2006-01), pages 83-91, XP002544327 ISSN: 1044-1549 the whole document</p>	1-12, 45-60, 83-91

INTERNATIONAL SEARCH REPORT

International application No.
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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 allsearchable 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.:

1-12, 45-60, 83-91
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.:

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: 1-12 and 91

A method of identifying an agent that inhibits H358 tumour cells from undergoing an epithelial to mesenchymal transition.

2. claims: 13-23 and 92

A method of identifying an agent that inhibits H358 tumor cells that have undergone an epithelial to mesenchymal transition.

3. claims: 24-35 and 93

A method of identifying an agent that stimulates mesenchymal-like H358 tumor cells to undergo a mesenchymal to epithelial transition.

4. claims: 36-38

A method of preparing a composition comprising a chemical compound which inhibits the growth of H358 tumor cells that have undergone an epithelial to mesenchymal transition.

5. claims: 39-44 and 94

A mesenchymal-like H358 tumor cell preparation for use in the identification of anti-cancer agents.

6. claims: 45-60

A method of identifying an agent that inhibits engineered H358 tumour cells from undergoing an epithelial to mesenchymal transition.

7. claims: 61-65

A method of identifying an agent that inhibits engineered H358 tumor cells that have undergone an epithelial to mesenchymal transition.

8. claims: 66-82

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of identifying an agent that stimulates mesenchymal-like engineered H358 tumor cells to undergo a mesenchymal to epithelial transition.

9. claims: 83-90

An engineered H358 tumour cell preparation for use in the identification of anti-cancer agents.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/001456

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007212738 A1	13-09-2007	WO 2008127718 A2	23-10-2008
US 2006211060 A1	21-09-2006	NONE	