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(54) Title: CELL MIGRATION INHIBITING COMPOSITIONS AND METHODS AND COMPOSITIONS FOR TREATING CANCER

(57) Abstract: Methods for treating an individual having cancer are provided. The method may include administering a cell migration inhibitor and a chemotherapeutic agent to the individual to inhibit migration of cancer cell. Inhibiting cell migration may increase cell division. In this manner, the cell migration inhibitor and the chemotherapeutic agent in combination may have increased efficacy compared to the chemotherapeutic agent alone due to the increased cell division. The cell migration inhibitor may include any of the inhibitors described herein. For example, the cell migration inhibitor may be an organic molecule having a molecular weight of less than about 700, a monoclonal antibody, or a natural product.



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INTERNATIONAL SEARCH REPORT

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PCT/US03/17399

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01N 33/53, 33/567; C12N 5/00

US CL : 435/7.1, 7.2, 7.21, 325, 395

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)

U.S. : 435/7.1, 7.2, 7.21, 325, 395

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, STN, MEDLINE, BIOSIS, CAPLUS, EMBASE WPIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,054,468 A (GEERTS et al) 25 April 2000 (25.04.2000), see entire patent, especially col. 2, lines 16-67, Example 3, col. 5, lines 35-col. 6, line 20.	1-13
Y	US 6,335,163 B1 (SHARON) 01 January 2002 (01.01.2002), see entire patent, especially col. 1, lines 15-30, col. 6, lines 17-33, col. 7, line 10-col. 9, line 11, col. 14, line 50-col. 15, line 54.	1-13
Y	US 2002/0048813 A1 (GERTLER et al) 25 April 2002 (25.04.2002), see entire patent, especially p. 3, para [0013]-[0014], p. 4, para [0029]-[0031], p. 8, para [0079]-p. 9, para [0088], p. 13, para [0115]-[0116], p. 15, para [0129]-[0130], and claims 17-24.	1-13
Y	MARIANI, L. et al. Glioma cell motility is associated with reduced transcription of proapoptotic and proliferation genes: a cDNA microarray analysis. Journal of Neuro-Oncology, 2001, Vol. 53, pages 161-176. See entire publication.	1-13
Y	HE, J. et al. Construction and Preliminary Screening of a Human Phage Single-Chain Antibody Library Associated with Gastric Cancer. Journal of Surgical Research, February 2002 (published online 27 November 2001), Vol. 102, 150-155. See entire publication.	1-13

☒ 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	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"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	"&" document member of the same patent family

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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BERENS, M.E. et al. The role of extracellular matrix in human astrocytoma migration and proliferation studied in a microliter scale assay. Clin. Exp. Metastasis, 1994, Vol. 12, pages 405-415, see entire publication.	1-13
Y	KRAMER, R.H. et al. Melanoma Cell Adhesion to Basement Membrane Mediated by Integrin-related Complexes. Cancer Research, 15 January 1989, Vol. 49, pages 393-402, see entire publication.	1-13

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International application No.

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 14-77 and 82-86
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:
Please See Continuation Sheet
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation 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 fee, this Authority did not invite payment of any additional fee.
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.: 1-13

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

Continuation of Box I Reason 2:

Claims 14-77 and 82-86 are independent claims and their dependent claims, where the independent claims are drawn to chemical formulas having variable groups, such as "R₁", however, the independent claims do not indicate values that the variables may have. Therefore claims 14-77 and 82-86 are unsearchable.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

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, claim(s) 1-13, drawn to methods for identifying a chemical selected from a library of chemicals, which inhibits cell migration comprising cancer cells, comprising using guided cell sedimentation, and a kit comprising a guided cell sedimentation apparatus.

Group II, claim(s) 78-81, drawn to methods for treating an individual having cancer, comprising administering a cell migration inhibitor and a chemotherapeutic agent.

Group III, claim(s) 87 and 88, drawn to methods for identifying a treatment for an individual having cancer comprising establishing a tissue culture of the cancer, identifying a cell migration inhibitor based on the tissue culture and identifying a chemotherapeutic agent that has efficacy in combination with the cell migration inhibitor.

Group IV, claim(s) 89-91, drawn to methods for treating an individual having cancer comprising administering a cell migration inhibitor.

Group V, claim(s) 92, drawn to methods for inhibiting cell migration comprising a cell migration inhibitor, wherein the inhibitor is an arylating agent.

Group VI, claim(s) 93, drawn to composition comprising a cell migration inhibitor and a chemotherapeutic agent, wherein the cell migration inhibitor is an arylating agent.

Group VII, claim(s) 94, drawn to methods treating an individual having cancer comprising administering a cell migration inhibitor, wherein the inhibitor is an arylating agent.

Group VIII, claim(s) 95 and 97, drawn to methods for inhibiting cancer cell migration, comprising treating cells with a cell migration inhibitor as claimed in claim 95.

Group IX, claim(s) 96, drawn to compositions comprising a cell migration inhibitor and a chemotherapeutic agent, wherein the migration inhibitor and agent are the migration inhibitor and chemotherapeutic agent as claimed in claim 96.

Group X, claim(s) 98, 100, 102, 103, 105 and 106, drawn to methods for treating or inhibiting breast cancer cell migration, comprising 4-methyl-3-nitro-benzoic acid.

Group XI, claim(s) 99, 101, 104, drawn to compositions comprising a cell migration inhibitor that is 4-methyl-3-nitro-benzoic acid and a chemotherapeutic agent.

Group XII, claim(s) 105, drawn to methods for treating an individual having cancer, comprising a cell migration inhibitor that is 4-methyl-3-nitro-benzoic acid.

Group XIII, claim(s) 107, drawn to methods for inhibiting pancreatic cancer cell migration, comprising treating pancreatic cancer cells with a cell migration inhibitor as claimed in claim 107.

Group XIV, claim(s) 108, drawn to methods for inhibiting pancreatic cancer cell migration, comprising treating pancreatic cancer cells with a cell migration inhibitor as claimed in claim 108.

Group XV, claim(s) 109, drawn to methods for inhibiting pancreatic cancer cell migration comprising treating cancer cells with a cell migration inhibitor as claimed in claim 109.

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Group XVI, claim(s) 110, drawn to methods for inhibiting pancreatic cancer cell migration, comprising treating pancreatic cancer cells with a cell migration inhibitor as claimed in claim 110.

Group XVII, claim(s) 111, drawn to methods for inhibiting pancreatic cancer cell migration, comprising treating pancreatic cancer cells with a cell migration inhibitor as claimed in claim 111.

Group XVIII, claim(s) 112, drawn to methods for inhibiting pancreatic cancer cell migration, comprising treating pancreatic cancer cells with a cell migration inhibitor as claimed in claim 112.

Group IXX, claim(s) 113, drawn to methods for inhibiting angiogenesis, comprising an inhibitor as claimed in claim 113.

Group XX, claim(s) 114, drawn to methods for inhibiting angiogenesis, comprising an inhibitor as claimed in claim 114.

Group XXI, claim(s) 115, drawn to methods for inhibiting angiogenesis, comprising an inhibitor as claimed in claim 115.

Group XXII, claim(s) 116, drawn to compositions comprising a cell migration inhibitor and a chemotherapeutic agent, wherein the migration inhibitor and agent are the migration inhibitor and chemotherapeutic agent as claimed in claim 116.

Group XXIII, claim(s) 117, drawn to methods for treating an individual having pancreatic cancer, comprising administering a cell migration inhibitor and a chemotherapeutic agent as claimed in claim 117.

Group XXIV, claim(s) 118, a pharmaceutical composition comprising 1-(4-chloro-benzoyl)-2-(4-methoxy-phenyl)-1,2-dihydro-3aH-pyrrolo[1,2-a]quinoline-3,3-dicarbonitrile and gemcytabine.

Group XXV, claim(s) 119, drawn to methods for treating an individual having pancreatic cancer, comprising administering a cell migration inhibitor and a chemotherapeutic agent as claimed in claim 119.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

A library of organic molecules or organic molecules having a molecular weight of less than about 700, or monoclonal antibodies or natural products

A cell migration inhibitor that is an organic molecule having a molecular weight of less than about 700, a monoclonal antibody or a natural product.

A disease comprising autoimmune disease or cardiovascular disease.

The claims are deemed to correspond to the species listed above in the following manner:

A library of organic molecules or organic molecules having a molecular weight of less than about 700, or monoclonal antibodies or natural products: Claims 5-9

A cell migration inhibitor that is an organic molecule having a molecular weight of less than about 700, a monoclonal antibody or a natural product: Claim 79-81

A disease comprising autoimmune disease or cardiovascular disease: Claim 90-91.

The following claim(s) are generic:

Claims 1, 78, and 89.

The inventions listed as Groups I-XXV 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:

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According to PCT Rule 13.2, unity of invention exists only when there is a shared same or corresponding special technical feature among the claimed inventions. The inventions listed as Groups I-XXVI do not relate to a single general inventive concept because they lack the same or corresponding special technical feature. Group I is directed to methods for identifying a chemical selected from a library of chemicals, which inhibits cell migration, that has the special technical feature of identifying a chemical that inhibits cell migration by using guided cell sedimentation, said special technical feature not being shared by any of the remaining groups. The technical feature of inhibiting cell migration or treating cancer, found in all Groups I-XXVI, (particularly Groups XII-XXVI), is anticipated by the prior art of Geerts et al., US 6,054,468 A, which discloses compounds and methods for inhibiting cancer cell migration using the chemical 1-(1H-pyrrol-2-ylmethyl)-2-piperidone (see, for example, col. 2, lines 16-67), and including cell tissue culture (Example 3, col. 5, line 35-col. 6, line 20), but Geerts et al. does not disclose using guided cell sedimentation. The remaining Groups II-XXVI are drawn to methods drawn to different objectives, e.g., as treating individual cancers, (such as pancreatic cancer), or inhibiting angiogenesis, or chemicals that do not share a common molecular core structure that substantially confers the property of inhibiting cell migration.

Therefore, the technical features of inhibiting cell migration, or methods of treatment, or inhibitors thereof, which links the inventions of Groups I-XXVI, does not constitute a special technical feature, as defined by PCT Rule 13.2, as it does not define a contribution over the prior art of Geerts et al., US 6,054,468 A. The special technical feature of identifying compounds that inhibit cell migration using guided cell sedimentation, linking the claims of Group I, is not found in the remaining groups and so is not a technical feature that links the remaining claims. The individual specific compounds of the claims are not technical features that link the claims, because the compounds do not share a common molecular core structure that substantially confers the property of cell migration inhibition.

The special technical feature of Group I is considered to be using guided cell sedimentation to identify a chemical that inhibits cell migration.

The technical feature of Group II is considered to be methods for treating an individual having cancer, comprising administering a cell migration inhibitor and a chemotherapeutic agent.

The technical feature of Group III is considered to be methods for identifying a treatment for an individual having cancer comprising establishing a tissue culture of the cancer, identifying a cell migration inhibitor based on the tissue culture and identifying a chemotherapeutic agent that has efficacy in combination with the cell migration inhibitor.

The technical feature of Group IV is considered to be methods for treating an individual having cancer comprising administering a cell migration inhibitor.

The technical feature of Group V is considered to be methods for inhibiting cell migration comprising a cell migration inhibitor, wherein the inhibitor is an arylating agent.

The technical feature of Group VI is considered to be compositions comprising a cell migration inhibitor and a chemotherapeutic agent, wherein the cell migration inhibitor is an arylating agent.

The technical feature of Group VII is considered to be methods treating an individual having cancer comprising administering a cell migration inhibitor, wherein the inhibitor is an arylating agent.

The technical feature of Group VIII is considered to be methods for inhibiting cancer cell migration, comprising treating cells with a cell migration inhibitor as claimed in claim 95.

The technical feature of Group IX is considered to be compositions comprising a cell migration inhibitor and a chemotherapeutic agent, wherein the migration inhibitor and agent are the migration inhibitor and chemotherapeutic agent as claimed in claim 96.

The technical feature of Group X is considered to be methods for treating or inhibiting breast cancer cell migration, comprising 4-methyl-3-nitro-benzoic acid.

The technical feature of Group XI is considered to be compositions comprising a cell migration inhibitor that is 4-methyl-3-nitro-benzoic acid and a chemotherapeutic agent.

The technical feature of Group XII is considered to be methods for treating an individual having cancer, comprising a cell migration inhibitor that is 4-methyl-3-nitro-benzoic acid.

The technical feature of Group XIII is considered to be methods for inhibiting pancreatic cancer cell migration, comprising treating pancreatic cancer cells with a cell migration inhibitor as claimed in claim 107.

The technical feature of Group XIV is considered to be methods for inhibiting pancreatic cancer cell migration, comprising treating pancreatic cancer cells with a cell migration inhibitor as claimed in claim 108.

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The technical feature of Group XV is considered to be methods for inhibiting pancreatic cancer cell migration comprising treating cancer cells with a cell migration inhibitor as claimed in claim 109.

The technical feature of Group XVI is considered to be methods for inhibiting pancreatic cancer cell migration, comprising treating pancreatic cancer cells with a cell migration inhibitor as claimed in claim 110.

The technical feature of Group XVII is considered to be methods for inhibiting pancreatic cancer cell migration, comprising treating pancreatic cancer cells with a cell migration inhibitor as claimed in claim 111.

The technical feature of Group XVIII is considered to be methods for inhibiting pancreatic cancer cell migration, comprising treating pancreatic cancer cells with a cell migration inhibitor as claimed in claim 112.

The technical feature of Group IXX is considered to be methods for inhibiting angiogenesis, comprising an inhibitor as claimed in claim 113.

The technical feature of Group XX is considered to be methods for inhibiting angiogenesis, comprising an inhibitor as claimed in claim 114.

The technical feature of Group XXI is considered to be methods for inhibiting angiogenesis, comprising an inhibitor as claimed in claim 115.

The technical feature of Group XXII is considered to be compositions comprising a cell migration inhibitor and a chemotherapeutic agent, wherein the migration inhibitor and agent are the migration inhibitor and chemotherapeutic agent as claimed in claim 116.

The technical feature of Group XXIII is considered to be methods for treating an individual having pancreatic cancer, comprising administering a cell migration inhibitor and a chemotherapeutic agent as claimed in claim 117.

The technical feature of Group XXIV is considered to be compositions comprising 1-(4-chloro-benzoyl)-2-(4-methoxy-phenyl)-1,2-dihydro-3aH-pyrrolo[1,2-a]quinoline-3,3-dicarbonitrile and gemcytabine.

The technical feature of Group XXV is considered to be methods for treating an individual having pancreatic cancer, comprising administering a cell migration inhibitor and a chemotherapeutic agent as claimed in claim 119.

Accordingly, Groups I-XXVI are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.