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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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(88) Date of publication of the international search report:
24 June 2010

(54) Title: METHODS AND SYSTEMS FOR PREDICTING RESPONSE OF CELLS TO A THERAPEUTIC AGENT

(57) Abstract: The invention provides methods for treating patients which methods comprise methods for predicting responses of cells, such as tumor cells, to treatment with therapeutic agents. These methods involve measuring, in a sample of the cells, levels of one or more components of a cellular network and then computing a Network Activation State (NAS) or a Network Inhibition State (NIS) for the cells using a computational model of the cellular network. The response of the cells to treatment is then predicted based on the NAS or NIS value that has been computed. The invention also comprises predictive methods for cellular responsiveness in which computation of a NAS or NIS value for the cells (e.g., tumor cells) is combined with use of a statistical classification algorithm. Biomarkers for predicting responsiveness to treatment with a therapeutic agent that targets a component within the ErbB signaling pathway are also provided.



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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68 C07K16/32

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)

C07K C12Q

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, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/015935 A (BAYER HEALTHCARE LLC; WIRTZ RALPH MARKUS [DE] BAYER HEALTHCARE LLC [US] 8 February 2007 (2007-02-08) the whole document	1-12,104
Y	ERJALA KAISA ET AL: "Signaling via ErbB2 and ErbB3 associates with resistance and epidermal growth factor receptor (EGFR) amplification with sensitivity to EGFR inhibitor gefitinib in head and neck squamous cell carcinoma cells." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 1 JUL 2006, vol. 12, no. 13, 1 July 2006 (2006-07-01), pages 4103-4111, XP002554455 ISSN: 1078-0432 the whole document	1-12,104



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 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

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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	EP 1 728 802 A (GENENTECH INC [US]) 6 December 2006 (2006-12-06) the whole document -----	1-12,104
Y	WO 97/35885 A (GENENTECH INC [US]) 2 October 1997 (1997-10-02) the whole document -----	1-12,104
Y	SCHOEBERL BIRGIT M ET AL: "Computational modeling and simulation lead to the development of MM-121, a human monoclonal antibody ErbB3 antagonist" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW YORK, NY, US, vol. 49, 1 April 2008 (2008-04-01), page 386, XP009125511 ISSN: 0197-016X the whole document -----	1-12,104
Y	SCHOEBERL BIRGIT M ET AL: "MM-121: a human monoclonal antibody ErbB3 antagonist" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW YORK, NY, US, vol. 49, 1 April 2008 (2008-04-01), page 944, XP009125512 ISSN: 0197-016X the whole document -----	1-12,104
P,X	WO 2008/100624 A (MERRIMACK PHARMACEUTICALS INC [US]; SCHOEBERL BIRGIT [US]; NIELSEN ULR) 21 August 2008 (2008-08-21) the whole document -----	1-12,104

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/054051

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.:

1-12, 104

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, 104

A method of treating a patient having neoplastic tumor according to claim 1.

2. claims: 13-103

A method of predicting the response of cells to a treatment with an agent, comprising identifying levels of one or more components measured in a sample of the cells, computing a Network activation State or a Network Inhibition State using a mechanistic computational model, and generating therefrom a predicted response of the cells to the treatment.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/054051

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2007015935	A	08-02-2007	EP 1913160 A2 US 2009298061 A1	23-04-2008 03-12-2009
EP 1728802	A	06-12-2006	NONE	
WO 9735885	A	02-10-1997	AT 342283 T AU 727082 B2 AU 2071197 A BR 9708343 A CA 2246429 A1 CN 1214695 A DE 69736806 T2 DK 0896586 T3 EP 0896586 A1 ES 2274537 T3 IL 126303 A JP 3925943 B2 JP 2000508526 T NZ 331360 A ZA 9702554 A	15-11-2006 30-11-2000 17-10-1997 03-08-1999 02-10-1997 21-04-1999 09-08-2007 19-02-2007 17-02-1999 16-05-2007 23-05-2002 06-06-2007 11-07-2000 27-03-2000 25-09-1998
WO 2008100624	A	21-08-2008	AU 2008216600 A1 CA 2678181 A1 CN 101674846 A CR 11029 A EC SP099637 A EP 2129396 A2 KR 20100014426 A US 2009291085 A1	21-08-2008 21-08-2008 17-03-2010 29-12-2009 28-12-2009 09-12-2009 10-02-2010 26-11-2009