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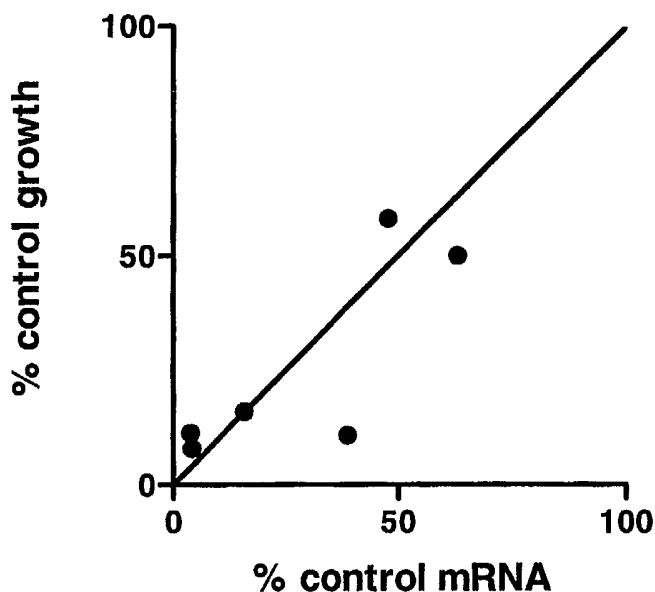
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[Continued on next page]

(54) Title: SYNTHETIC LETHAL SCREEN USING RNA INTERFERENCE



(57) Abstract: The invention provides a method for identifying one or more genes in a cell of a cell type which interact with, e.g., modulate the effect of, an agent, e.g., a drug. For example, an identified gene may confer resistance or sensitivity to a drug, i.e., reduces or enhances the effect of the drug. The invention also provides STK6 and TPX2 as a gene that exhibits synthetic lethal interactions with KSP encoding a kinesin-like motor protein, and methods and compositions for treatment of diseases, e.g., cancers, by modulating the expression of STK6 or TPX2 gene and/or the activity of STK6 or TPX2 gene product. The invention also provides genes involved in cellular response to DNA damage, and their therapeutic uses.

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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US2004/031629

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 C12Q1/68		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 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, BIOSIS, EMBASE, FSTA		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DEVERAUX QUINN L ET AL: "Exposing oncogenic dependencies for cancer drug target discovery and validation using RNAi." SEMINARS IN CANCER BIOLOGY. AUG 2003, vol. 13, no. 4, August 2003 (2003-08), pages 293-300, XP002325031 ISSN: 1044-579X figure 2 page 297, right-hand column - page 298, right-hand column ----- -/--	1-3
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		
<input checked="" type="checkbox"/> Patent family members are listed in 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 document but 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	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search  <div style="text-align: center; font-weight: bold;">3 May 2005</div>	Date of mailing of the international search report  <div style="text-align: center; font-weight: bold;">25. 07. 2005</div>	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  <div style="text-align: center; font-weight: bold;">Leber, T</div>	

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US2004/031629

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 02/072783 A (IRM, LLC; CALDWELL, JEREMY, S; CHANDA, SUMIT, K; SOMIA, NIKUNJ, V; HOG) 19 September 2002 (2002-09-19) claims 1,17,18,65 page 13, line 28 - page 14, line 13 page 6, lines 5-10</p> <p>-----</p>	18,20, 115,116
A	<p>WO 02/44321 A (MAX-PLANCK-GESELLSCHAFT ZUR FOERDERUNG DER WISSENSCHAFTEN E.V; TUSCHL,) 6 June 2002 (2002-06-06)</p> <p>-----</p>	
A	<p>US 2003/170642 A1 (CALDWELL JEREMY S ET AL) 11 September 2003 (2003-09-11)</p> <p>-----</p>	
A	<p>US 2003/165945 A1 (BIRD TIMOTHY A ET AL) 4 September 2003 (2003-09-04)</p> <p>-----</p>	
A	<p>HANNON G J: "RNA interference" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 418, 11 July 2002 (2002-07-11), pages 244-251, XP002979088 ISSN: 0028-0836</p> <p>-----</p>	
A	<p>HOLEN T ET AL: "Positional effects of short interfering RNAs targeting the human coagulation trigger Tissue Factor" NUCLEIC ACIDS RESEARCH, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 30, no. 8, 15 April 2002 (2002-04-15), pages 1757-1766, XP002232890 ISSN: 0305-1048</p> <p>-----</p>	

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2004/031629

## Box 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 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 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.:

1-41, 115-136

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- 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: 1-41,115-136

Methods for identifying a gene whose product modulates the effect of an agent on a cell or cell type comprising a cell comprising at least one siRNA to a target gene and measuring the cellular response in comparison to the cells not having any siRNA but being exposed to the agent.

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2. claims: 137-157

A method for evaluating the responsiveness of a cell to a drug comprising  
a) contacting a cell or cell type which comprises at least one siRNA to a primary target gene with a drug and, additionally, with a composition that modulates the expression of a secondary target gene  
b) contacting cell or cell type which DO NOT comprises any siRNA to a primary target gene with a drug and, additionally, with a composition that modulates the expression of a secondary target gene, and  
c) comparing the cellular response of cells in a) and b).

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3. claims: 42-114,158-164

This invention refers to methods of treatments of cancer, screening methods, kits affecting the expression of genes and/or relating to the genes STK6 or TPX2 or KSP inhibitors.

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4. claims: 165-218

This invention relates to methods for evaluating the sensitivity of cells to DNA damaging agents, to methods for screening for agents affecting the sensitivity to DNA damaging agents and to cells, arrays and kits relating to genes involved in the sensitivity of cells to DNA damaging agents.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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