

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 September 2004 (30.09.2004)

PCT

(10) International Publication Number
WO 2004/083240 A3

(51) International Patent Classification⁷: C07K 14/47,
C12N 15/11, A61K 48/00, A61P 35/00

(21) International Application Number:
PCT/GB2004/001128

(22) International Filing Date: 17 March 2004 (17.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0306148.8 18 March 2003 (18.03.2003) GB

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

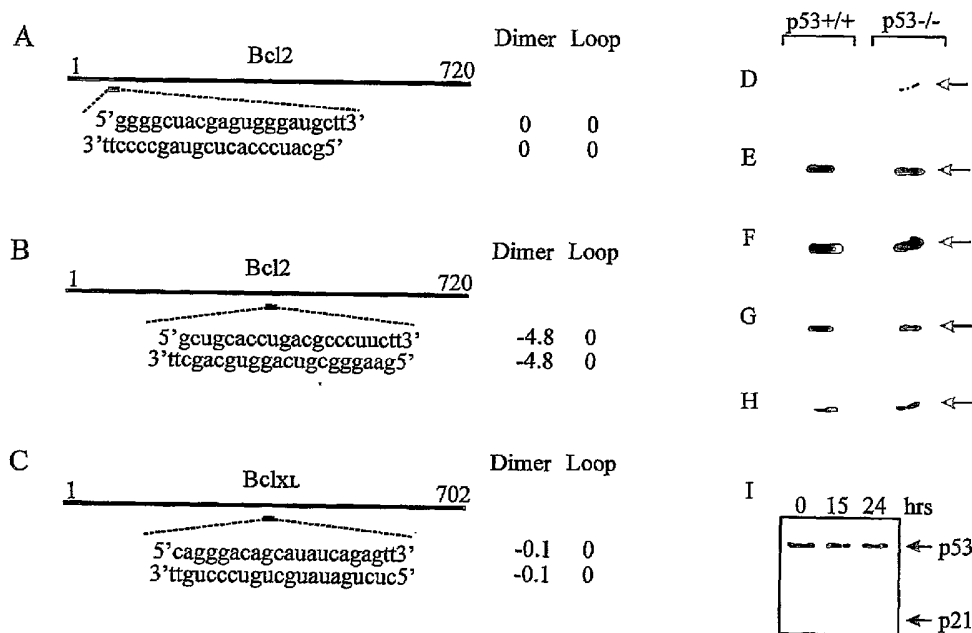
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report

(88) Date of publication of the international search report:
24 March 2005

[Continued on next page]

(54) Title: REGULATION OF GENE EXPRESSION



(57) Abstract: The present invention relates to a method of regulating apoptosis. The method comprises the step of introducing into a cell an RNA construct comprising a nucleotide sequence which is homologous to mRNA within said cell. The mRNA within the cell includes genetic information of a gene element involved in the regulation of apoptosis. The invention also relates to an siRNA construct having a nucleotide sequence which is homologous to mRNA transcribed from a gene element involved in the regulation of apoptosis.

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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

 Int. Application No
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A. CLASSIFICATION OF SUBJECT MATTER		
IPC 7	C07K14/47	C12N15/11 A61K48/00 A61P35/00
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)		
IPC 7 C07K C12N A61K		
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, WPI Data, PAJ		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CIOCA DANIEL P ET AL: "RNA interference is a functional pathway with therapeutic potential in human myeloid leukemia cell lines." CANCER GENE THERAPY, vol. 10, no. 2, February 2003 (2003-02), pages 125-133, XP002293680 ISSN: 0929-1903 page 126, left-hand column, last paragraph - right-hand column, paragraph 1 figures 1,3	1-4, 7-11, 15-18
Y	page 132, left-hand column, paragraph 3 ----- -/--	19
<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 *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. *Z* document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report	
26 October 2004	08. 11. 2004	
Name and mailing address of the ISA	Authorized officer	
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	ALCONADA RODRIGUEZ	

INTERNATIONAL SEARCH REPORT

In: International Application No
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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.
X	FUTAMI TAKASHI ET AL: "Induction of apoptosis in HeLa cells with siRNA expression vector targeted against bcl-2." NUCLEIC ACIDS RESEARCH. SUPPLEMENT (2001) 2002, no. 2, 2002, pages 251-252, XP002264267	1-4, 7-11, 15-20
Y	abstract	19
X	WO 02/055692 A (VORNLOCHER HANS-PETER ; LIMMER STEFAN (DE); RIBOPHARMA AG (DE); GEICK) 18 July 2002 (2002-07-18) page 5, lines 17-26 page 7, lines 18-22 page 3, lines 19-33 page 6, lines 10-26	1,2, 5-10,13, 15-18
Y	GAUTSCHI O ET AL: "ACTIVITY OF A NOVEL BCL-2/BCL-XL-BISPECIFIC ANTISENSE OLIGONUCLEOTIDE AGAINST TUMORS OF DIVERSE HISTOLOGIC ORIGINS" JOURNAL OF THE NATIONAL CANCER INSTITUTE, US DEPT. OF HEALTH, EDUCATION AND WELFARE, PUBLIC HEALTH, US, vol. 93, no. 6, 21 March 2001 (2001-03-21), pages 463-471, XP009003270 ISSN: 0027-8874 figures 2-4	19
A	US 6 414 134 B1 (REED JOHN C) 2 July 2002 (2002-07-02) the whole document	
P,X	WO 03/070969 A (MCSWIGGEN JAMES ; BEIGELMAN LEONID (US); SIRNA THERAPEUTICS INC (US)) 28 August 2003 (2003-08-28) page 7, lines 17-20; examples 4-10; tables II,III	1-5, 7-11,13, 15-20
P,X	WACHECK VOLKER ET AL: "Small interfering RNA targeting Bcl-2 sensitizes malignant melanoma." OLIGONUCLEOTIDES, vol. 13, no. 5, October 2003 (2003-10), pages 393-400, XP001189796 ISSN: 1545-4576 page 394, right-hand column, paragraph 2; figures 4,5	1-4, 7-11, 15-18
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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.
P,X	<p>JIANG MING ET AL: "Bcl-2 constitutively suppresses p53-dependent apoptosis in colorectal cancer cells." GENES AND DEVELOPMENT, vol. 17, no. 7, 1 April 2003 (2003-04-01), pages 832-837, XP002293683 ISSN: 0890-9369 the whole document</p>	1-4, 7-12, 15-20
P,X	<p>CAO XIAOBO X ET AL: "A short-interfering RNA (siRNA) duplex targeted to BCL-XL significantly reduces BCL-XL expression and enhances response to chemotherapy in mesothelioma." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 44, July 2003 (2003-07), page 1098, XP001182915 & 94TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH; WASHINGTON, DC, USA; JULY 11-14, 2003 ISSN: 0197-016X abstract</p>	1,2, 5-10, 13-20
P,X	<p>ZENDER L ET AL: "Small interfering RNA (siRNA) and antisense oligonucleotides (ASO) for reversion of chemotherapy resistance in hepatoma cells." JOURNAL OF HEPATOLOGY, vol. 38, no. Supplement 2, April 2003 (2003-04), page 107, XP002301756 & 38TH ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER; INSTANBUL, TURKEY; MARCH 29-APRIL 01, 2003 ISSN: 0168-8278 abstract</p>	1,2, 5-10,13, 15-18
P,X	<p>WALTEMATHE M ET AL: "Essential role for bcl-xl as an antiapoptotic factor in TRAIL mediated apoptosis of hepatocytes during viral infection." JOURNAL OF HEPATOLOGY, vol. 38, no. Supplement 2, April 2003 (2003-04), page 107, XP002301757 & 38TH ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER; INSTANBUL, TURKEY; MARCH 29-APRIL 01, 2003 ISSN: 0168-8278 abstract</p>	1,2, 5-10,13, 15-18
P,X	<p>WO 03/040366 A (HAREL-BELLAN ANNICK ; DAUTRY FRANCOIS (FR); AIT-SI-ALI SLIMANE (FR); C) 15 May 2003 (2003-05-15) claims 14,15,28,31</p>	1,2,5, 7-10,13, 15-18

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International application No.

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

a. type of material

a sequence listing

table(s) related to the sequence listing

b. format of material

in written format

in computer readable form

c. time of filing/furnishing

contained in the international application as filed

filed together with the international application in computer readable form

furnished subsequently to this Authority for the purpose of search

2. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

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national application No.
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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:

Although claims 1-7, as far as relating to an in vivo method, and claims 15 and 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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.:

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: 1,2,7-10, 15-20 (in part) and 3, 4,11, 12 (complete)

A siRNA construct which is homologous to the Bcl-2 mRNA; method of regulating apoptosis and of treating diseases associated with inappropriate apoptosis by introducing said siRNA into a cell.

2. claims: 1,2,7-10, 15-20 (in part) and 5, 6, 13, 14 (complete)

As invention 1 but relating to an siRNA construct which is homologous to the Bcl-XL mRNA.

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/JP2004/001128

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Int'l Patent Application No
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