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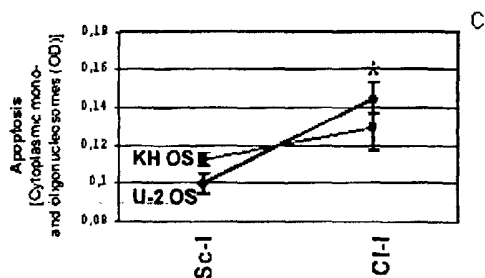
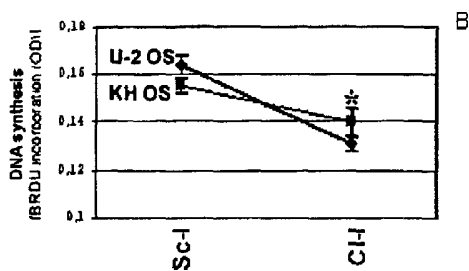
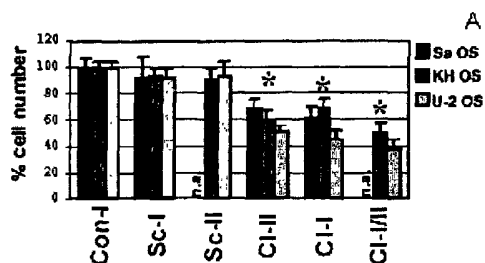
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[Continued on next page]

(54) Title: RNAI PROBES TARGETING CANCER-RELATED PROTEINS



(57) Abstract: RNAi sequences that are useful as therapeutics in the treatment of cancers of various types, including prostate cancer, sarcomas such as osteosarcoma, renal cell carcinoma, breast cancer, bladder cancer, lung cancer, colon cancer, ovarian cancer, anaplastic large cell lymphoma and melanoma; and Alzheimer's disease. These sequences target clusterin, IGFBP-5, IGFBP-2, both IGFBP-2 and -5 simultaneously, Mitf, and B-raf. The invention further provides for the use of these RNAi sequences in the treatment of cancers of various types, including prostate cancer, sarcomas such as osteosarcoma, renal cell carcinoma, breast cancer, bladder cancer, lung cancer, colon cancer, ovarian cancer, anaplastic large cell lymphoma and melanoma; and Alzheimer's disease, and a method of treating such conditions through the administration of the RNA molecules with RNAi activity to an individual, including a human individual in need of such treatment.

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(81) **Designated States (national):** AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), 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, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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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

national Application No  
PCT/CA 03/01277

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C12N15/11 A61K31/712

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 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, WPI Data, EMBASE, CHEM ABS Data, BIOSIS, MEDLINE

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A	WO 00/49937 A (UNIV BRITISH COLUMBIA ;GLEAVE MARTIN (CA); RENNIE PAUL S (CA); MIY) 31 August 2000 (2000-08-31) cited in the application the whole document ---	
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Further documents are listed in the continuation of box C.

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

12 May 2004

Date of mailing of the international search report

26. 05. 04

Name and mailing address of the ISA

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International Application No  
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Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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International Application No

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G.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	HARBORTH J ET AL: "Identification of essential genes in cultured mammalian cells using small interfering RNAs" JOURNAL OF CELL SCIENCE, ESSEX, GB, vol. 114, no. PART 24, December 2001 (2001-12), pages 4557-4565, XP002247988 ---	
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International Application No  
PCT/CA 03/01277

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>FIRE A ET AL: "Potent and specific genetic interference by double-stranded RNA in <i>Caenorhabditis elegans</i>" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 391, 19 February 1998 (1998-02-19), pages 806-811, XP002095876 ISSN: 0028-0836</p> <p style="text-align: center;">---</p>	
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A	<p>PADDISON P J CAUDY A A HANNON G J: "Stable suppression of gene expression by RNAi in mammalian cells" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 99, no. 3, 5 February 2002 (2002-02-05), pages 1443-1448, XP002958887 ISSN: 0027-8424</p> <p style="text-align: center;">---</p>	
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INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CA 03/01277

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	<p>BRUMMELKAMP THIJN R ET AL: "A system for stable expression of short interfering RNAs in mammalian cells" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 296, no. 5567, 19 April 2002 (2002-04-19), pages 550-553, XP002234902 ISSN: 0036-8075</p>	
A	<p>SUI GUANGCHAO ET AL: "A DNA vector-based RNAi technology to suppress gene expression in mammalian cells" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 99, no. 8, 16 April 2002 (2002-04-16), pages 5515-5520, XP002964701 ISSN: 0027-8424</p>	
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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CA 03/01277

C<sub>2</sub> (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 00/69454 A (CHAKRABARTY SHILA ;SINGH POMILA (US); UNIV TEXAS (US)) 23 November 2000 (2000-11-23) ---	
A	PAVELIC JASMINKA ET AL: "Insulin-like growth factor family and combined antisense approach in therapy of lung carcinoma" MOLECULAR MEDICINE (BALTIMORE), vol. 8, no. 3, March 2002 (2002-03), pages 149-157, XP002276629 ISSN: 1076-1551 ---	
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA 03/01277

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 13-17 partially  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2.  Claims Nos.: 1-3, 10-16 partially  
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:  
see FURTHER INFORMATION sheet PCT/ISA/210
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 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:

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.:  
1-3, 10-16 partially; 4, 5, 7, 17 completely
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: 1-3,10-16 partially; 4,17 completely

RNA molecules effective for blocking translation of or degrading a mRNA that is the transcriptional product of a target gene, the target gene being clusterin, and their use in the treatment of cancer and Alzheimer disease.

2. Claims: 1-3, 10-16 partially; 5 completely

RNA molecules effective for blocking translation of or degrading a mRNA that is the transcriptional product of a target gene, the target gene being IGFBP2, and their use in the treatment of cancer and Alzheimer disease.

3. Claims: 1-3,10-16 partially; 6 completely

RNA molecules effective for blocking translation of or degrading a mRNA that is the transcriptional product of a target gene, the target gene being IGFBP5, and their use in the treatment of cancer and Alzheimer disease.

4. Claims: 1-3,10-16 partially; 7 completely

RNA molecules effective for blocking translation of or degrading a mRNA that is the transcriptional product of a target gene, the target genes being IGFBP2 and IGFBP5 simultaneously, and their use in the treatment of cancer and Alzheimer disease.

5. Claims: 1-3,10-16 partially; 8 completely

RNA molecules effective for blocking translation of or degrading a mRNA that is the transcriptional product of a target gene, the target gene being Mitf, and their use in the treatment of cancer and Alzheimer disease.

6. Claims: 1-3, 10-16 partially; 9 completely

RNA molecules effective for blocking translation of or degrading a mRNA that is the transcriptional product of a target gene, the target gene being B-raf, and their use in the treatment of cancer and Alzheimer disease.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 13-17 are directed to methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.1

Claims Nos.: 13-17 partially

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Claims Nos.: 1-3, 10-16 partially

Present claims 1-3 relate to a RNA molecule defined by reference to a desirable characteristic or property, namely that it has "a sequence effective to mediate degradation or block translation of mRNA that is the transcriptional product of a gene, wherein the target gene is selected from among genes encoding clusterin, IGFBP-5, IGFBP-2, both IGF-BP-2 and 5 simultaneously, MITF, and B-raf" (result to be achieved). The claims cover all RNA molecules having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such RNA molecules. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the RNA molecules specifically referred to in claims 4-9.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No

PCT/CA 03/01277

Patent document cited in search report		Publication date	Patent family member(s)	Publication date			
WO 0222635	A	21-03-2002	US 6383808 B1	07-05-2002			
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