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IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,  
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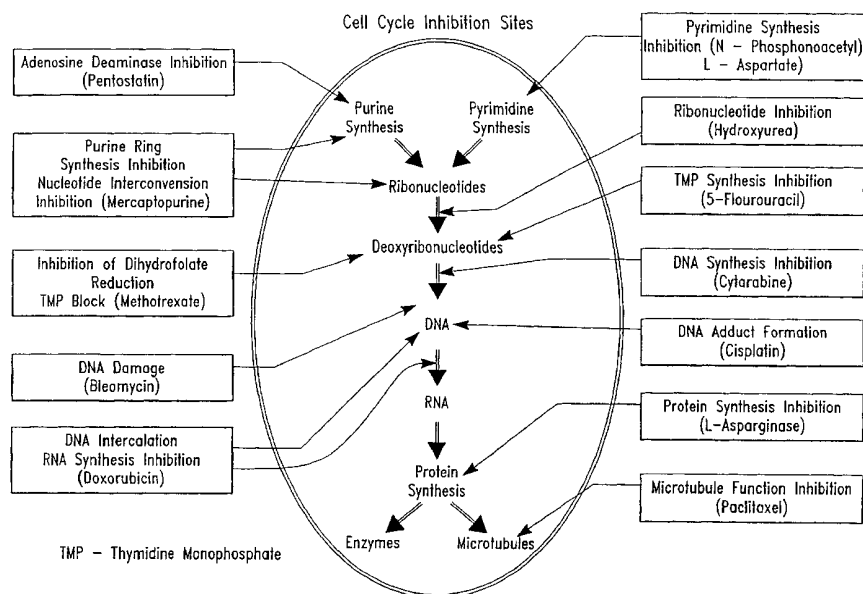
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[Continued on next page]

(54) Title: COMPOSITIONS OF A COMBINATION OF RADIOACTIVE THERAPY AND CELL-CYCLE INHIBITORS



(57) Abstract: Disclosed herein are therapeutic devices, compositions and methods for treating proliferative diseases. For example, within one aspect of the invention therapeutic devices are provided, comprising a device that locally administers radiation, and a cell-cycle inhibitor.



(88) Date of publication of the international search report:  
4 July 2002

*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/CA 00/01333

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K51/12 A61K31/335 A61K41/00 A61N5/10 A61N5/10  
 //(A61K41/00,31:335)

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 A61K A61N

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)

EP0-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 93 14787 A (UNIV COLUMBIA)<br>5 August 1993 (1993-08-05)<br><br>figures<br>tables                                                                                                                                                                                                                                                                                                                             | 1-16,<br>19-211,<br>213-354 |
| Y          | ---<br>BECKER A ET AL: "Phase I-II study of<br>simultaneous radiotherapy and paclitaxel<br>(taxol) in a twice a week (TIW) schedule<br>for recurrent squamous cell carcinomas of<br>the head and neck (SCCHN)"<br>EUROPEAN JOURNAL OF CANCER, PERGAMON<br>PRESS, OXFORD, GB,<br>vol. 33, September 1997 (1997-09), page<br>S193, abstract no. 872, XP004283720<br>ISSN: 0959-8049<br>abstract<br><br>---<br>-/-- | 1-16,<br>19-211,<br>213-354 |

☒ 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.

"&" document member of the same patent family

Date of the actual completion of the international search

27 November 2001

Date of mailing of the international search report

17. 04. 2002

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01333

## 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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| Y          | ZANELLI G D ET AL: "Paclitaxel as a Radiosensitiser: A Proposed Schedule of Administration Based on In Vitro Data and Pharmacokinetic Calculations"<br>EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB,<br>vol. 33, no. 3, March 1997 (1997-03),<br>pages 486-492, XP004282474<br>ISSN: 0959-8049<br>abstract<br>page 487, left-hand column<br>tables<br>figures<br>--- | 1-16,<br>19-211,<br>213-354 |
| Y          | FORMENTI C ET AL: "Concurrent paclitaxel and radiation in locally advanced breast cancer"<br>EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB,<br>vol. 34, 30 September 1998 (1998-09-30),<br>page S12, abstract no. 39 XP004285179<br>ISSN: 0959-8049<br>abstract<br>---                                                                                                | 1-16,<br>19-211,<br>213-354 |
| P,Y        | LI C ET AL: "POTENTIATION OF OVARIAN OCA-1 TUMOR RADIORESPONSE BY POLY (L-GLUTAMIC ACID)-PACLITAXEL CONJUGATE"<br>INTERNATIONAL JOURNAL OF RADIATION: ONCOLOGY BIOLOGY PHYSICS, PERGAMON PRESS, US,<br>vol. 48, no. 4,<br>1 November 2000 (2000-11-01), pages<br>1119-1126, XP001023465<br>ISSN: 0360-3016<br>the whole document<br>---                                        | 1-16,<br>19-211,<br>213-354 |
| Y          | MOTE P A ET AL: "PACLITAXEL SENSITIZES MULTIDRUG RESISTANT CELLS TO RADIATION"<br>ANTI-CANCER DRUGS, OXFORD, GB,<br>vol. 7, no. 2,<br>1 February 1996 (1996-02-01), pages<br>182-188, XP002074267<br>ISSN: 0959-4973<br>page 183, right-hand column, paragraph 2<br>figures<br>page 187, right-hand column, paragraph<br>CONCLUSIONS -page 188<br>---<br>-/--                  | 1-16,<br>19-211,<br>213-354 |

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International Application No

PCT/CA 00/01333

## 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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| Y          | MILAS L ET AL: "ENHANCEMENT OF TUMOR RADIORESPONSE OF A MURINE BY PACLITAXEL" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 54, 1994, pages 3506-3510, XP000882929<br>ISSN: 0008-5472<br>abstract<br>page 3307; table 1<br>page 3308, right-hand column, last paragraph<br>---                                                                                                                        | 1-16,<br>19-211,<br>213-354 |
| Y          | WO 95 03036 A (ANGIOGENESIS TECH INC ;ARSENAULT A LARRY (CA); BURT HELEN M (CA);) 2 February 1995 (1995-02-02)<br>example 9<br>---                                                                                                                                                                                                                                                                                                         | 1-16,<br>19-211,<br>213-354 |
| Y          | WO 96 25176 A (RENO JOHN M ;KUNZ LAWRENCE L (US); NEORX CORP (US))<br>22 August 1996 (1996-08-22)<br>claims 4,8,11,18,27,32,36,45,49,53,57,61<br>---                                                                                                                                                                                                                                                                                       | 1-16,<br>19-211,<br>213-354 |
| Y          | WO 98 43618 A (NEORX CORP)<br>8 October 1998 (1998-10-08)<br><br>example 18<br>---                                                                                                                                                                                                                                                                                                                                                         | 1-16,<br>19-211,<br>213-354 |
| Y          | KORNOWSKI RAN ET AL: "Slow-release taxol coated GRII stents reduce neointima formation in a porcine coronary in-stent restenosis model." 70TH SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION;ORLANDO, FLORIDA, USA; NOVEMBER 9-12, 1997, vol. 96, no. 8 SUPPL., 1997, page I341<br>XP000891206<br>Circulation 10/21/97, 1997<br>ISSN: 0009-7322<br>abstract<br>---                                                                  | 1-16,<br>19-211,<br>213-354 |
| Y          | HAEHNEL I ET AL: "Local growth inhibitory effect of paclitaxel release by a biodegradable stent coating on vascular smooth muscle cells." 47TH ANNUAL SCIENTIFIC SESSION OF THE AMERICAN COLLEGE OF CARDIOLOGY;ATLANTA, GEORGIA, USA; MARCH 29-APRIL 1, 1998, vol. 31, no. 2 SUPPL. A, February 1998 (1998-02), page 278A<br>XP000877498<br>Journal of the American College of Cardiology Feb., 1998<br>ISSN: 0735-1097<br>abstract<br>--- | 1-16,<br>19-211,<br>213-354 |
|            | ---                                                                                                                                                                                                                                                                                                                                                                                                                                        |                             |
|            | -/--                                                                                                                                                                                                                                                                                                                                                                                                                                       |                             |

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01333

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                              | Relevant to claim No.       |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Y          | FARB ANDREW ET AL: "Paclitaxel polymer-coated stents reduce neointima." 70TH SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION;ORLANDO, FLORIDA, USA; NOVEMBER 9-12, 1997, vol. 96, no. 8 SUPPL., 1997, page I608 XP000891207 Circulation 10/21/97, 1997 ISSN: 0009-7322 abstract<br>---                                                                                                                                                                    | 1-16,<br>19-211,<br>213-354 |
| Y          | HAEHNEL I ET AL: "Local growth inhibitory effect of paclitaxel released by a biodegradable stent coating on vascular smooth muscle cells." XIXTH CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY TOGETHER WITH THE 32ND ANNUAL GENERAL MEETING OF THE ASSOCIATION OF EUROPEAN PAEDIATRIC CARDIOLOGISTS;STOCKHOLM, SWEDEN; AUGUST 24-28, 1997, vol. 18, no. ABSTR. SUPPL., 1997, page 460 XP000877497 European Heart Journal 1997 ISSN: 0195-668X abstract<br>--- | 1-16,<br>19-211,<br>213-354 |
| Y          | MANIFOLD D K ET AL: "Taxol coated stents in oesophageal adenocarcinoma." DIGESTIVE DISEASE WEEK AND THE 99TH ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION;NEW ORLEANS, LOUISIANA, USA; MAY 16-22, 1998, vol. 114, no. 4 PART 2, 15 April 1998 (1998-04-15), page A27 XP000891205 Gastroenterology April 15, 1998 ISSN: 0016-5085 abstract<br>---                                                                                              | 1-16,<br>19-211,<br>213-354 |
| Y          | VOISARD R ET AL: "Paclitaxel-coated biodegradable stents inhibit proliferative activity and severely damage cytoskeletal components of smooth muscle cells from human coronary plaque material in vitro." XXTH CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY;VIENNA, AUSTRIA; AUGUST 22-26, 1998, vol. 19, no. ABST. SUPPL., August 1998 (1998-08), page 376 XP000891208 European Heart Journal Aug., 1998 ISSN: 0195-668X abstract<br>---<br>-/--             | 1-16,<br>19-211,<br>213-354 |

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01333

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                                                                            | Relevant to claim No.       |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Y          | <p>HAEHNEL IRIS ET AL: "Differential effect of a local paclitaxel release from a biodegradable stent coating on vascular smooth muscle cells and endothelial cells in a coculture model."</p> <p>48TH ANNUAL SCIENTIFIC SESSION OF THE AMERICAN COLLEGE OF CARDIOLOGY;NEW ORLEANS, LOUISIANA, USA; MARCH 7-10, 1999, vol. 33, no. 2 SUPPL. A, February 1999 (1999-02), page 222A<br/>XP000877499<br/>Journal of the American College of Cardiology Feb., 1999<br/>ISSN: 0735-1097<br/>abstract</p> <p>---</p> | 1-16,<br>19-211,<br>213-354 |
| Y          | <p>DE 197 54 870 A (ALT ECKHARD PROF DR)<br/>6 August 1998 (1998-08-06)</p> <p>claims</p> <p>-----</p>                                                                                                                                                                                                                                                                                                                                                                                                        | 1-16,<br>19-211,<br>213-354 |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA 00/01333

## 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.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 182-354 are directed to a method of treatment of the human/animal body, a search has been carried out, based on the alleged effects of the device/combination.
2. ☒ Claims Nos.: 1-16, 19-211 and 213-354 in part, and 17, 18 and 212  
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.:
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.:  
  
1-15, 19-210, 213-354 partially, and 16, 211

### 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: 1-15, 19-210, 213-354 in part, and 16, 211

Devices and methods for the combined therapeutic use of radiation and a cell-cycle inhibitor, in which the cell-cycle inhibitor is the taxane paclitaxel

2. Claims: 1-15, 19-210, 213-247, 249-272, 274-277, 279-287, 289-310, 312-329, 331-337, 339-345, 347-353 in part, and 17, 212

Devices and methods for the combined therapeutic use of radiation and a cell-cycle inhibitor, in which the cell-cycle inhibitor is the topoisomerase inhibitor camptothecin or irinotecan

3. Claims: 1-15, 18-210, 213-247, 249-263, 265-329, 331-337, 339-354 in part

Devices and methods for the combined therapeutic use of radiation and a cell-cycle inhibitor, in which the cell-cycle inhibitor is the alkylating agent dacarbazine

4. Claims: 1-15, 18-210, 213-247, 249-263, 265-354 in part

Devices and methods for the combined therapeutic use of radiation and a cell-cycle inhibitor, in which the cell-cycle inhibitor is the nitrogen mustard alkylating agent ifosfamide

5. Claims: 1-15, 18-210, 213-247, 249-329, 331-337, 339-354 in part

Devices and methods for the combined therapeutic use of radiation and a cell-cycle inhibitor, in which the cell-cycle inhibitor is the nitrosurea alkylating agent carmustine or lomustine

6. Claims: 1-15, 18-210, 213-239, 241-254, 256-277, 279-299, 301-310, 312-345, 347-354 in part

Devices and methods for the combined therapeutic use of radiation and a cell-cycle inhibitor, in which the cell-cycle inhibitor is the antimetabolite 5-fluorouracil

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. Claims: 1-15,18-210, 213-254, 256-277, 279-299, 301-310, 312-345, 347-354 in part

Devices and methods for the combined therapeutic use of radiation and a cell-cycle inhibitor, in which the cell-cycle inhibitor is the antimetabolite methotrexate, or the structurally related folinic acid (leucovorine)

8. Claims: 1-15,18-210, 213-239, 241-254, 256-277, 279-299, 301-345, 347-354 in part

Devices and methods for the combined therapeutic use of radiation and a cell-cycle inhibitor, in which the cell-cycle inhibitor is the antimetabolite gemcitabine or cytarabine, or the structurally related floxuridine.

9. Claims: 1-15,18-210, 213-229, 231-239, 241-277, 279-299, 301-310, 312-345, 347-354 in part

Devices and methods for the combined therapeutic use of radiation and a cell-cycle inhibitor, in which the cell-cycle inhibitor is the vinca alkaloid vincristine or its sulfate

10. Claims: 1-15,19-210, 213-229, 231-345, 347-354 in part

Devices and methods for the combined therapeutic use of radiation and a cell-cycle inhibitor, in which the cell-cycle inhibitor is the platinum compound cisplatin

11. Claims: 1-15,19-210, 213-229, 231-254, 256-263, 265-287, 289-299, 301-329, 331-337, 339-345, 347-353 in part

Devices and methods for the combined therapeutic use of radiation and a cell-cycle inhibitor, in which the cell-cycle inhibitor is mitomycin

12. Claims: 1-15,19-210, 213-229, 231-239, 241-263, 265-277, 279-287, 289-345, 347-354 in part

Devices and methods for the combined therapeutic use of radiation and a cell-cycle inhibitor, in which the

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

cell-cycle inhibitor is the anthracycline doxorubicin

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-16, 19-211 and 213-354 in part, and 17, 18 and 212

In view of the large number and also the wording of the claims presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that the possibility to perform a meaningful search is severely impaired.

Moreover, the pharmacologically active compounds mentioned in present claims 1-16, 19-211 and 213-354 are mainly defined by reference to a desirable characteristic or property, namely their ability to act as a cell-cycle inhibitor. The claims cover all compounds 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 compositions containing such compounds. 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. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope 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 compounds contained in the compositions prepared in the examples.

Remark: the present objection is raised only in the framework of the first invention, as defined under the objection for lack of unity. For the remaining inventions, similar objections are likely to be raised.

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

International Application No

PCT/CA 00/01333

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s)                                                                                                                                                                                                                                                                                                                                                                                               | Publication<br>date                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------|---|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| WO 9314787                                | A | 05-08-1993          | CA 2128693 A1<br>WO 9314787 A1<br>AU 2333892 A<br>EP 0624096 A1<br>JP 7506341 T<br>US 6080777 A                                                                                                                                                                                                                                                                                                                          | 05-08-1993<br>05-08-1993<br>01-09-1993<br>17-11-1994<br>13-07-1995<br>27-06-2000                                                                                                                                                                                                                                                                           |
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