



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|   |                  |  |
|---|------------------|--|
| <p>(51) International Patent Classification <sup>6</sup> :<br/><b>A61K 9/12, 31/00</b></p>  | <p><b>A3</b></p> | <p>(11) International Publication Number: <b>WO 98/29110</b><br/>(43) International Publication Date: 9 July 1998 (09.07.98)</p>   |
| <p>(21) International Application Number: PCT/US97/24289<br/>(22) International Filing Date: 30 December 1997 (30.12.97)<br/>(30) Priority Data:<br/>60/033,789 30 December 1996 (30.12.96) US<br/>(71) Applicant (for all designated States except US): BATTELLE MEMORIAL INSTITUTE [US/US]; 505 King Avenue, Columbus, OH 43201-2693 (US).<br/>(72) Inventors; and<br/>(75) Inventors/Applicants (for US only): PLACKE, Michael, E. [US/US]; 1473 Inglis Avenue, Columbus, OH 43212 (US). OMONDI, Anthony, R. [US/US]; 4515 Ravine Drive, Westerville, OH 43081 (US). BOOKER, Michael, J. [US/US]; 8381 Africa Road, Westerville, OH 43082 (US). FRYE, John, E. [US/US]; 191 Walnut Street, Groveport, OH 43125-1233 (US). SHAH, Praful, K. [US/US]; 4750 Coolbrook Drive, Hilliard, OH 43026 (US). FLANAGAN, Douglas, R., Jr. [US/US]; 1258 Dover Street, Iowa City, IA 52240-2829 (US). DONOVAN, Maureen, D. [US/US]; 2748 Lakeview Drive, N.E., Solon, IA 52333-9563 (US).</p> |                  | <p>(74) Agents: GOLDSTEIN, Steven, J. et al.; Frost &amp; Jacobs, 2500 PNC Center, 201 East Fifth Street, Cincinnati, OH 45202 (US).<br/>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b><br/><i>With international search report.<br/>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report:<br/>15 April 1999 (15.04.99)</p> |
| <p>(54) Title: FORMULATION AND METHOD FOR TREATING NEOPLASMS BY INHALATION</p>  |                  |  |
| <p>(57) Abstract</p> <p>A formulation, method, and apparatus for treating neoplasms such as cancer by administering a pharmaceutically effective amount of highly toxic composition by inhalation, wherein the composition is a non-encapsulated antineoplastic drug.</p>   |                  |  |

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/24289

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 A61K9/12 A61K31/00

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 6 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)

**C. 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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| X        | US 5 565 478 A (KOHN ET AL.)<br>15 October 1996                                    | 1-4, 7-9,<br>20-28,<br>65,<br>67-70,<br>77-84,<br>90-92,<br>107-112,<br>127 |
| Y        | see column 5 - column 6<br><br>---   | 43-64,<br>93-106  |

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
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Date of the actual completion of the international search

24 February 1999

Date of mailing of the international search report

**03.03.99**

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/24289

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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|-----------------------|---|--|
| X                     | WO 93 17665 A (SIEVERS ET AL.)<br>16 September 1993   | 1-4,7-9,<br>20-28,<br>65,<br>67-70,<br>77-84,<br>90-92,<br>107-112,<br>127 |
| Y                     | see page 3, paragraph 2   | 43-64,<br>93-106   |
| Y                     | see page 9, paragraph 1   |  |
| X                     | US 4 560 774 A (PETTIT ET AL.)<br>24 December 1985  | 1  |
| Y                     | see column 14, line 21 - line 26; example<br>10   | 43-64,<br>93-106   |
| X                     | SHEVCHENKO ET AL.: "Inhalation of<br>chemical substances and oxygen in<br>radiotherapy of bronchial cancer"<br>NEOPLASMA,<br>vol. 15, no. 4, 1968, pages 419-426,<br>XP002078721  | 1,93,94  |
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| Y                     | see page 421, paragraph 4   |  |
| X                     | TATSUMURA ET AL.: "Further evaluation of<br>the efficacy of nebulization chemotherapy<br>in the treatment of lung cancer"<br>CHEST,<br>vol. 106, no. 2 suppl., 1994, page 70s<br>XP002078722                              | 1  |
| Y                     | see abstract  | 43-64,<br>93-106   |
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| X                     | Database Cancerlit accession no. 71800442<br>& Ochanomizu Med. J., 18(3), p.103-114,<br>1970<br>XP002078724   | 1  |
| Y                     | cited in the application<br>see abstract  | 43-64,<br>93-106   |
| Y                     | see abstract  |  |
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| Y                     | see abstract  |  |
| Y                     | see abstract  |  |
| Y                     | see abstract  |  |
| Y                     | see abstract  |  |
| Y                     | see abstract  |  |
| Y                     | see abstract  |  |

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/24289

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          | see page 51 - page 53; claims 6-8  | 43-64,<br>93-106   |
| X          | ---  |  |
| X          | US 4 975 421 A (WILLIAMS DAVID L ET AL)<br>4 December 1990                         | 1,5-8,<br>11-16,<br>23-28,<br>37,<br>65-70,<br>80-87,<br>91,92,<br>113,127 |
| Y          | see column 18 - column 19  | 43-64,<br>93-106   |
| X          | ---  |  |
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| Y          | see column 5   | 43-64,<br>93-106   |
| Y          | see column 11  |  |
| X          | ---  |  |
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| Y          | see column 21 - column 22  | 43-64,<br>93-106   |
| X          | ---  |  |
| X          | US 5 268 164 A (KOZARICH JOHN W ET AL)<br>7 December 1993                          | 1-3,5-8,<br>10-13,<br>23-28,<br>65-71,<br>80-85,<br>91,92,<br>113,127      |
| Y          | see column 3, paragraph 3  | 43-64,<br>93-106   |
| Y          | see column 8   |  |
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| -/--       | -/--   |  |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/24289

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        | see page 7, paragraph 4<br>see page 10, paragraph 1   | 43-64,<br>93-106      |
| X        | <p style="text-align: center;">---</p> T.TATSAMURA ET AL.: "Further study of nebulisation chemotherapy, a new chemotherapeutic method in the treatment of lung carcinomas: fundamental and clinical"<br>BR.J.CANCER,<br>vol. 68, no. 6, 1993, pages 1146-1149,<br>XP002094448<br>cited in the application | 1                     |
| Y        | see abstract  | 43-64,<br>93-106      |
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| Y        | <p style="text-align: center;">---</p> & T.TATSAMURA ET AL.: "New chemotherapeutic method for the treatment of tracheal and bronchial cancers--nebulization chemotherapy"<br>GAN NO RINSHO,<br>vol. 29, no. 7, 1983, pages 765-770,   | 94-106                |
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| Y        | see abstract  | 95-106                |
| X        | WO 93 21938 A (ADRIA LAB) 11 November 1993  | 43-50                 |
| Y        | see page 15, line 15 - page 17, line 13   | 51-64                 |
| X        | <p style="text-align: center;">---</p> CRAIG LEWIS: "A review of the use of chemoprotectants in cancer chemotherapy"<br>DRUG SAFETY,<br>vol. 11, no. 3, 1994, pages 153-162,<br>XP002094514   | 43-50,52              |
| Y        | see the whole document  | 51,53-64              |
| X        | <p style="text-align: center;">---</p> G.T.BUDD ET AL.: "Clinical effects of amifostine (Ethyol) in patients treated with carboplatin"<br>EUR J CANCER,<br>vol. 32A, no. suppl. 4, 1996, pages<br>S43-S45, XP002094515  | 43-50                 |
| Y        | see abstract  | 51-64                 |
|          | <p style="text-align: center;">---</p> -/--   |                       |

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/24289

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        | US 5 438 072 A (BOBEE JEAN-MARC ET AL)<br>1 August 1995<br>see claims 1-5<br>---   | 29-36                 |
| Y        | EP 0 645 145 A (SQUIBB BRISTOL MYERS CO)<br>29 March 1995<br>see claims 1-17<br>---  | 29-36                 |
| Y        | C.LI ET AL.: "Synthesis and evaluation of<br>PEG-paclitaxel conjugate as a water<br>soluble paclitaxel prodrug"<br>PROC ANNU MEET AM ASSOC CANCER RES,<br>vol. 37, 1996, page 376 XP002094516<br>see abstract<br>----- | 29-36                 |

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 97/24289

**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:
  
- 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 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.:  
  
1-16, 20-37, 40-73, 77-87, 90-112, 127
  
- 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: 1-4,7-9,20-28,65,67-70,77-84,90-92,107-112,  
127 all in part in so far as taxanes are concerned

Formulations for inhalation containing taxanes and method of treatment involving these compositions

2. Claims: 1-3,4,7,8,10,65,67-70,  
107-  
112 all in part in so far as carboplatin is concerned

Formulations for inhalation containing carboplatin and method of treatment involving these compositions

3. Claims: 1,5,6,7,8,11,12,13,23-28,65,66-71,80-85,91,92,113,  
127 in so far as anthracyclines are concerned

Formulations for inhalation containing anthracyclines or doxorubicin and method of treatment involving these compositions

4. Claims: 1,5,6,7,8,14-16,23-28,65-70,72-73,80-84,86,87,  
91-92,113,  
127 in so far as vinca alkaloids are concerned

Formulations for inhalation containing vinca alkaloids and method of treatment involving these compositions

5. Claims: 1,17,74,78

Formulations for inhalation containing mechlorethamine and method of treatment involving these compositions

6. Claims: 1,17,74,88

Formulations for inhalation containing mithramycin and method of treatment involving these compositions

7. Claims: 1,17,74,88

Formulations for inhalation containing dactinomycin and method of treatment involving these compositions

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

8. Claims: 1,18,75,89

Formulations for inhalation containing bisantrene and method of treatment involving these compositions

9. Claims: 1,19,76,89

Formulations for inhalation containing amsacrine and method of treatment involving these compositions

10. Claims: 1,37,65

Formulations for inhalation containing carmustine and method of treatment involving these compositions

11. Claims: 1,37,65

Formulations for inhalation containing dacarbazine and method of treatment involving these compositions

12. Claims: 1,37,65

Formulations for inhalation containing melphalan and method of treatment involving these compositions

13. Claims: 1,37,65

Formulations for inhalation containing mercaptopurine and method of treatment involving these compositions

14. Claims: 1,37,65

Formulations for inhalation containing mitoxantrone and method of treatment involving these compositions

15. Claims: 1,37,65

Formulations for inhalation containing esorubicin and method of treatment involving these compositions

16. Claims: 1,37,65

Formulations for inhalation containing teniposide and method of treatment involving these compositions

17. Claims: 1,37,65

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Formulations for inhalation containing aclacinomycin and method of treatment involving these compositions

18. Claims: 1,37,65

Formulations for inhalation containing plicamycin and method of treatment involving these compositions

19. Claims: 1,37,65

Formulations for inhalation containing streptozocin and method of treatment involving these compositions

20. Claims: 1,37,65

Formulations for inhalation containing menogaril and method of treatment involving these compositions

21. Claims: 1,38,65

Formulations for inhalation containing estramustine phosphate and method of treatment involving these compositions

22. Claims: 1,38,65

Formulations for inhalation containing geldanamycin and method of treatment involving these compositions

23. Claims: 1,38,65

Formulations for inhalation containing bryostatin and method of treatment involving these compositions

24. Claims: 1,38,65

Formulations for inhalation containing suramin and method of treatment involving these compositions

25. Claims: 1,38,65

Formulations for inhalation containing carboxamido-triazoles and method of treatment involving these compositions

26. Claims: 1,38,65

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Formulations for inhalation containing onconase and method of treatment involving these compositions

27. Claims: 1,38,65

Formulations for inhalation containing SU101 or SU20 and method of treatment involving these compositions

28. Claims: 39,40,42

Formulations for inhalation containing etoposide and a DMA carrier

29. Claim : 41

Formulation for inhalation containing 9-aminocamptothecin

30. Claims: 29-36

Formulations containing taxanes and PEG and an alcohol as vehicles

31. Claims: 43-64

Formulations containing an antineoplastic drug and a chemoprotectant and method for treatment involving these compositions

32. Claims: 93-106

Method of treatment involving administering an antineoplastic drug by inhalation and administering the same or a different drug parenterally or by isolated organ perfusion

33. Claims: 114-123

Apparatus for treating a patient by inhalation containing an anticancer drug

34. Claims: 124-126

Inhalation mask for administering aerosols

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Patent Application No

PCT/US 97/24289

| Patent document cited in search report      | A | Publication date | Patent family member(s) | Publication date |
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