

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
28 March 2002 (28.03.2002)

PCT

(10) International Publication Number
WO 2002/024216 A3

(51) International Patent Classification⁷: **A61K 45/00**,
38/17, 38/30, A61P 35/00 // A61K 45:00, 38:17

(21) International Application Number:
PCT/US2001/029188

(22) International Filing Date:
18 September 2001 (18.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/233,840 19 September 2000 (19.09.2000) US

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

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(88) Date of publication of the international search report:
15 July 2004

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR USE OF IGF-BINDING PROTEIN FOR SELECTIVE SENSITIZATION OF TARGET CELLS *IN VIVO*

(57) Abstract: New methods for the treatment of human disease are provided. IGFBP-3 is administered together with a co-admin-
istered agent to subjects having disease, thereby alleviating the symptoms of the disease, under conditions where administration of
IGFBP-3 alone at the maximum practicable dose has no measurable beneficial effect on the disease condition.



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INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K45/00 A61K38/17 A61K38/30 A61P35/00
//A61K45:00,38:17

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 A61P

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, MEDLINE, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | US 5 840 673 A (SEIZINGER BERND R ET AL) 24 November 1998 (1998-11-24) column 2, line 9 - line 24 column 4, line 32 - line 58 claims 1-4 | 1-22 |
| X | ----- FOWLER C A ET AL: "IGFBP-3 and -5 have opposing actions on paclitaxel induced apoptosis of human breast cancer cells, Hs578T." GROWTH HORMONE AND IGF RESEARCH, vol. 9, no. 5, October 1999 (1999-10), page 368, XP009005668 5th International Symposium on Insulin-Like Growth Factors; Brighton, England, UK; October 31-November 4, 1999 ISSN: 1096-6374 the whole document ----- -/- | 1-22 |

☒ 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
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- "O" document referring to an oral disclosure, use, exhibition or other means
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- "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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- "&" document member of the same patent family

Date of the actual completion of the international search

7 June 2004

Date of mailing of the international search report

1.1.06.2004

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/29188

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>PORTERA C A JR ET AL: "Targeting the insulin-like growth factor axis in the therapy of colorectal carcinoma liver metastasis."</p> <p>GROWTH HORMONE & IGF RESEARCH: OFFICIAL JOURNAL OF THE GROWTH HORMONE RESEARCH SOCIETY AND THE INTERNATIONAL IGF RESEARCH SOCIETY. SCOTLAND APR 2000, vol. 10 Suppl A, April 2000 (2000-04), pages S47-S48, XP009005667 ISSN: 1096-6374 cited in the application column 2, paragraph 2</p> | 1-22 |
| X | <p>US 6 015 786 A (MASCARENHAS DESMOND ET AL) 18 January 2000 (2000-01-18) column 4, line 49 - line 57 column 11, line 66 - column 12, line 5</p> | 1,3,21,22 |
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| X | <p>US 6 017 885 A (ROSEN DAVID M ET AL) 25 January 2000 (2000-01-25) column 7, line 54 - column 8, line 7 column 9, line 44</p> | 1-3,6,21,22 |
| Y | <p>RAJAH ROOPMATHY ET AL: "IGFBP-3 mediates TNF-alpha induced apoptosis in the prostate cancer cell line, PC-3: Role of bcl-2 phosphorylation." PROSTATE, vol. 38, no. 4, March 1999 (1999-03), pages 352-353, XP009005670 International Symposium on Biology of Prostate Growth; Bethesda, Maryland, USA; March 15-18, 1998 ISSN: 0270-4137 the whole document</p> | 1-22 |

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/29188

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|----------------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No.***** |
| A | BUCKBINDER L ET AL: "INDUCTION OF THE GROWTH INHIBITOR IGF-BINDING PROTEIN 3 BY P53" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 377, no. 6550, 19 October 1995 (1995-10-19), pages 646-649, XP002025927 ISSN: 0028-0836 the whole document | |
| P,X | ----- DE 199 51 824 A (FORSSMANN WOLF GEORG) 3 May 2001 (2001-05-03) claims 1,24 | 1,3,21, 22 |
| P,Y | ----- FOWLER C A ET AL: "Insulin-like growth factor binding protein-3 (IGFBP-3) potentiates paclitaxel-induced apoptosis in human breast cancer cells." INTERNATIONAL JOURNAL OF CANCER, vol. 88, no. 3, 2000, pages 448-453, XP002230887 ISSN: 0020-7136 page 449, column 2, paragraph 7 page 452, column 1, paragraph 2 - column 2 ----- | 1-22 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/29188

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 1-20 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.: 1, 3, 4 (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:

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

Continuation of Box I.2

Claims Nos.: 1, 3, 4 (partially)

Present claims 1, 3, 4 relate to an extremely large number of possible "co-administered agents or treatment regimens" which are to be combined with IGFBP-3. In fact, the claims contain so many possibilities that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely the chemotherapeutic agents of claim 2, and in particular those of claim 6.

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/US 01/29188

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