

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
4 December 2003 (04.12.2003)

PCT

(10) International Publication Number
WO 2003/100429 A3

(51) International Patent Classification⁷: **G01N 33/574**,
33/68, C07K 16/18

(21) International Application Number:
PCT/CA2003/000752

(22) International Filing Date: 22 May 2003 (22.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/382,340 23 May 2002 (23.05.2002) US

(71) Applicant (for all designated States except US): **SUNNY-BROOK AND WOMEN'S COLLEGE HEALTH SCIENCES CENTRE** [CA/CA]; S-133, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5 (CA).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **FILMUS, Jorge** [CA/CA]; Sunnybrook and Women's College Health

Sciences Centre, 2075 Bayview Avenue, Room S218, Toronto, Ontario M4N 3M5 (CA). **CAPURRO, Mariana** [AR/CA]; Sunnybrook and Women's College Health Sciences Centre, 2075 Bayview Avenue, Room S218, Toronto, Ontario M4N 3M5 (CA).

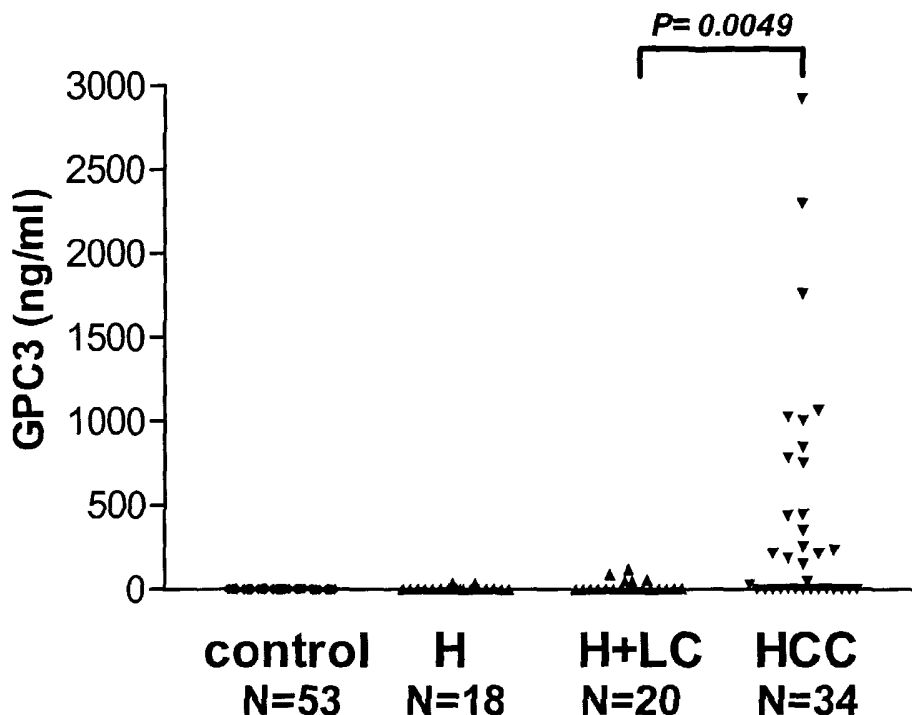
(74) Agent: **RAE, Patricia, A.**; Sim & McBurney, 330 University Avenue, 6th Floor, Toronto, Ontario M5G 1R7 (CA).

(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, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,

[Continued on next page]

(54) Title: DIAGNOSIS OF HEPATOCELLULAR CARCINOMA



(57) Abstract: A method is provided for screening a subject for hepatocellular carcinoma by determining the level of glypican-3 (GPC3) in a body fluid sample from the subject. A further method is provided for diagnosing hepatocellular carcinoma by detecting GPC3 in a liver tissue sample. Also provided are antibodies which bind specifically to GPC3.



SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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.

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:

19 February 2004

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 03/00752

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/574 G01N33/68 C07K16/18

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 G01N C07K

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, PAJ, EMBASE, BIOSIS, SEQUENCE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Capurro M.I. et al. : Overexpression of glypican-3 in human hepatocellular carcinomas determined by immunohistochemistry using a monoclonal antibody. Proceedings of the American Association for Cancer Research Annual Meeting, March 2002, vol. 43, page 219, Abstract Number : 1097 XP002957172 the whole document --- -/--	1,5-37

☒ 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

12 November 2003

Date of mailing of the international search report

16/12/2003

Name and mailing address of the ISA

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

Authorized officer

Giry, M

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 03/00752

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHU Z.-W. ET AL.: "Enhanced glypican-3 expression differentiates the majority of hepatocellular carcinomas from benign hepatic disorders." GUT, vol. 48, 2001, pages 558-564, XP002959808 cited in the application the whole document	1,5-37
X	TREVISANI F. ET AL.: "Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status." J. HEPATOL., vol. 34, 2001, pages 570-575, XP002261240 the whole document	2-4
P,X	SUNG Y.-K. ET AL.: "Glypican-3 is overexpressed in human hepatocellular carcinoma." CANCER SCI., vol. 94, no. 3, March 2003 (2003-03), pages 259-262, XP002261241 the whole document	1-37
P,X	WO 03 000883 A (CHUGAI SEIYAKU KABUSHIKI KAISHA) 3 January 2003 (2003-01-03) the whole document	1,5-37
T	CAPURRO M. ET AL.: "Glypican-3: a novel serum and histochemical marker for hepatocellular carcinoma." GASTROENTEROLOGY, vol. 125, no. 1, July 2003 (2003-07), pages 89-97, XP009020918 the whole document	1-37
T	NAKATSURA T. ET AL.: "Glypican-3, overexpressed specifically in human hepatocellular carcinoma, is a novel tumor marker." BIOCHEM. BIOPHYS. RES. COMM., vol. 306, 19 June 2003 (2003-06-19), pages 16-25, XP002261242 the whole document	1-37
A	WO 00 23109 A (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 27 April 2000 (2000-04-27) the whole document	1-37

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 03/00752

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 37764 A (VLAAMS INTERUNIVERSITAIR INSTITUUT VOOR BIOTECHNOLOGIE) 29 July 1999 (1999-07-29) the whole document ----	1-37
A	HSU H.-C. ET AL.: "Cloning and expression of a developmentally regulated transcript MXR7 in hepatocellular carcinoma: biological significance and temporospatial distribution." CANCER RES., vol. 57, 15 November 1997 (1997-11-15), pages 5179-5184, XP002956383 cited in the application abstract; table 1 ----	1,5-37
A	SHERMAN M.: "Alphafetoprotein: an obituary." J. HEPATOL., vol. 34, 2001, pages 603-605, XP002261243 cited in the application the whole document -----	2-4

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-17 and 25-28, due to the steps of "obtaining a body fluid sample from the subject" (claims 1-17) or of "obtaining a liver tissue sample from the subject" (claims 25-28) are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 1-17, 25-28

Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 03/00752

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.: 1-17, 25-28
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.:
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:

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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No

PCT/CA 03/00752

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03000883	A	03-01-2003	WO 03000883 A1	03-01-2003
WO 0023109	A	27-04-2000	AU 1118100 A	08-05-2000
			CA 2346264 A1	27-04-2000
			EP 1146903 A1	24-10-2001
			WO 0023109 A1	27-04-2000
			US 2003103980 A1	05-06-2003
WO 9937764	A	29-07-1999	AU 2422999 A	09-08-1999
			WO 9937764 A2	29-07-1999