

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
26 February 2004 (26.02.2004)

PCT

(10) International Publication Number
WO 2004/016813 A3

(51) International Patent Classification⁷: **C12Q 1/68**

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(21) International Application Number:

PCT/IB2003/003516

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(22) International Filing Date: 14 August 2003 (14.08.2003)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

02292054.0

16 August 2002 (16.08.2002) EP

(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, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, 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, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

— with international search report

(88) Date of publication of the international search report:

22 July 2004

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.

(54) Title: HNF1 ALPHA AS A TUMOR SUPPRESSOR GENE, AND DIAGNOSTIC AND THERAPEUTIC APPLICATIONS THEREOF

(57) Abstract: The present invention relates to diagnostic methods and therapeutics in the field of tumors involving Hepatocyte Nuclear Factor 1a (HNF1a). The invention provides an in vitro method for the diagnosis of a tumor in a patient, which method comprises determining the expression or activity of HNF1a. The invention also provides a HNF1a gene therapy and protein therapy method.



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INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/03516

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

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 C12Q

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, MEDLINE, EMBASE, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KALKUHL A ET AL: "Expression of hepatocyte-enriched nuclear transcription factors in mouse liver tumours." CARCINOGENESIS. ENGLAND MAR 1996, vol. 17, no. 3, March 1996 (1996-03), pages 609-612, XP008016972 ISSN: 0143-3334 the whole document -----	1,2,4-6, 9-12, 19-21
Y	XU L ET AL: "Expression profiling suggested a regulatory role of liver-enriched transcription factors in human hepatocellular carcinoma." CANCER RESEARCH. UNITED STATES 1 APR 2001, vol. 61, no. 7, 1 April 2001 (2001-04-01), pages 3176-3181, XP002243262 ISSN: 0008-5472 the whole document ----- -/--	1,2,4-6, 9-12, 19-21



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

"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

19 December 2003

Date of mailing of the international search report

16. 04. 2004

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INTERNATIONAL SEARCH REPORT

Inter

Application No

PCT/IB 03/03516

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ANASTASIADIS A G ET AL: "Loss of function of the tissue specific transcription factor HNF1 alpha in renal cell carcinoma and clinical prognosis." ANTICANCER RESEARCH. GREECE 1999 MAY-JUN, vol. 19, no. 3A, May 1999 (1999-05), pages 2105-2110, XP008016973 ISSN: 0250-7005 the whole document -----	1,2,4-6, 9,10, 19-21
Y	SEL S ET AL: "Human renal cell carcinogenesis is accompanied by a coordinate loss of the tissue specific transcription factors HNF4 alpha and HNF1 alpha." CANCER LETTERS. IRELAND 29 MAR 1996, vol. 101, no. 2, 29 March 1996 (1996-03-29), pages 205-210, XP002243263 ISSN: 0304-3835 the whole document -----	1,2,4-6, 9,10, 19-21
A	ELLARD S: "Hepatocyte nuclear factor 1 alpha (HNF-1 alpha) mutations in maturity-onset diabetes of the young." HUMAN MUTATION. UNITED STATES NOV 2000, vol. 16, no. 5, November 2000 (2000-11), pages 377-385, XP008016982 ISSN: 1098-1004 the whole document -----	
A	VAXILLAIRE M ET AL: "Identification of nine novel mutations in the hepatocyte nuclear factor 1 alpha gene associated with maturity-onset diabetes of the young (MODY3)." HUMAN MOLECULAR GENETICS. ENGLAND APR 1997, vol. 6, no. 4, April 1997 (1997-04), pages 583-586, XP002243264 ISSN: 0964-6906 the whole document -----	
A	AIHARA T ET AL: "Clonal analysis of precancerous lesion of hepatocellular carcinoma." GASTROENTEROLOGY. UNITED STATES AUG 1996, vol. 111, no. 2, August 1996 (1996-08), pages 455-461, XP008017099 ISSN: 0016-5085 the whole document -----	

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INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/IB 03/03516

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BACH I ET AL: "Cloning of human hepatic nuclear factor 1 (HNF1) and chromosomal localization of its gene in man and mouse." GENOMICS. UNITED STATES SEP 1990, vol. 8, no. 1, September 1990 (1990-09), pages 155-164, XP008017098 ISSN: 0888-7543 the whole document -----	
A	BOCCACCIO C ET AL: "Chromosomal localization and sequence analysis of a human episomal sequence with in vitro differentiating activity." SOMATIC CELL AND MOLECULAR GENETICS. UNITED STATES MAY 1994, vol. 20, no. 3, May 1994 (1994-05), pages 163-170, XP008017100 ISSN: 0740-7750 the whole document -----	
P,X	BLUTEAU OLIVIER ET AL: "Bi-allelic inactivation of TCF1 in hepatic adenomas." NATURE GENETICS. UNITED STATES OCT 2002, vol. 32, no. 2, October 2002 (2002-10), pages 312-315, XP002243265 ISSN: 1061-4036 the whole document -----	1-14,16, 19-21
P,X	LAURENT-PUIG PIERRE ET AL: "Frequent mutations of hepatocyte nuclear factor 1 in colorectal cancer with microsatellite instability." GASTROENTEROLOGY. UNITED STATES MAY 2003, vol. 124, no. 5, May 2003 (2003-05), pages 1311-1314, XP001157544 ISSN: 0016-5085 the whole document -----	1-10,15, 17-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/03516

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.:
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.:

1-21

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: 1-21

An in vitro method for the diagnosis of a tumor in a patient, which method comprises determining the expression or activity of HNF1alpha in a biological sample; a method for determining the susceptibility of a subject to develop a colon tumor, which method comprises detecting a polymorphism consisting of a 864G>C transversion in the HNF1alpha gene; use of a nucleic acid encoding a functional HNF1alpha protein or a functional HNF1alpha protein, for the preparation of a medicament.

2. claim: 22

A method for determining the toxicity of an estroprogestative agent on genomic DNA which method comprises
a) contacting an estroprogestative agent to be tested with a DNA sequence that encodes HNF1alpha or with a cell expressing HNF1alpha;
b) determining the effect of the estroprogestative agent on the DNA sequence that encodes HNF1alpha or on the expression or activity of HNF1alpha.
