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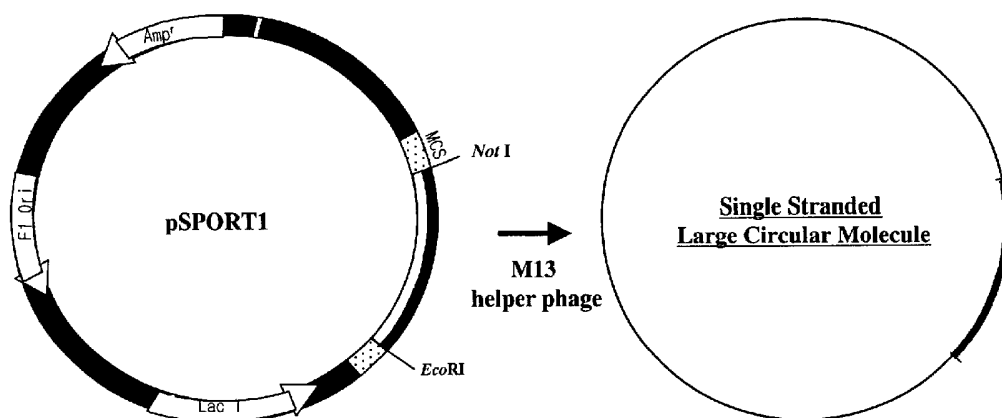
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ning of each regular issue of the PCT Gazette.

(54) Title: LARGE CIRCULAR SENSE MOLECULE ARRAY



**Single strand rescue by infection with helper
bacteriophages**

(57) Abstract: Large circular (LC)-sense molecules in an array is disclosed. The LC-sense molecules array is combined with cDNA hybridization to detect differences in expression profile between different cells. LC-sense molecules were purified from nonredundant clones with recombinant phagemid and arrayed onto silanized slide glasses. By hybridization of LC-sense array with Cy3 or Cy5-labelled cDNA preparations at 60 °C, 29 up-regulated and 6 down-regulated genes in cancerous liver tissue were detected.

WO 2004/013277 A3

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER					
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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) SEE ELECTRONIC DATABASE BOX BELOW					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched SEE ELECTRONIC DATABASE BOX BELOW					
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) [WPIDS] [MEDLINE] [CA]: BACTERIOPHAGE; PHAGE?; LARGE CIRC?; LARGE CIRCULAR; SINGLE STRAND?; PROBE; HYBRISIZ?; HYBRIDIS?; SCREEN?; ?ARRAY; ?CHIP; MEMBRANE; ?BEAD; SENSE; SOLID SUPPORT; RNA; DNA; NUCLEIC ACID; POLYNUCLEOTIDE; NUCLEIC ACID HYBRIDIZATION.					
C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.			
X	WO 1999/000520 A1 (THE GOVERNMENT OF THE UNITED STATES OF AMERICA, REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES) 7 January 1999. See the entire document, and in particular pages 13-17 and 20.	1-18			
X	US 2002/0055099 A1 (PAUL B FISHER) 9 May 2002. See the entire document.	1-18			
☒ Further documents are listed in the continuation of Box C ☒ See patent family annex					
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> * 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 application or patent 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 </td> <td style="width: 33%; vertical-align: top;"> "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 </td> <td style="width: 33%;"></td> </tr> </table>			* 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 application or patent 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	
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2003/004955

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Drmanac R et al (1992). Sequencing by hybridization: towards an automated sequencing of one million M13 clones arrayed on membranes. Electrophoresis 13: 566-573. See the entire document.	1-18
X	WO 2001/000786 A2 (SPRING DIAGNOSTICS LTD) 4 January 2001. See the entire document, and in particular claims 34 and 35.	1-18
X	Drmanac S and Drmanac R (1994). Processing of cDNA and genomic kilobase-size clones for massive screening, mapping and sequencing by hybridization. Biotechniques 17(2): 328-9, 332-6. See the entire document.	1-18
X	Kainz P et al (1989). A modified primer extension procedure for specific detection of DNA-RNA hybrids on nylon membranes. Analytical Biochemistry 179: 366-370. See the entire document.	1-18

Supplemental Box

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

The international application does not comply with the requirements of unity of invention under Rule 13 of the PCT, because the application does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept. It is a requirement under Rule 13 of the PCT that the claims shall define a single invention, where all claims are linked by a common special technical feature. A special technical feature is defined as being a feature that provides an advance over the prior art. The present claims do not conform to this requirement.

In coming to this conclusion the International Searching Authority has found that there are 31 different inventions as follows:

1. Claims 1-18 (all completely) are directed towards arrays or libraries of large circular (LC) sense nucleic acids. It is considered that the provision of arrays or libraries of LC-sense molecules comprises a first "special technical feature".
2. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of cytochrome P450, subfamily IIE (ethanol-inducible) (GenBank Accession Number J02843). It is considered that the detection of up regulation of cytochrome P450, subfamily IIE (ethanol-inducible) (GenBank Accession Number J02843) comprises a second "special technical feature".
3. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of transcription elongation factor A (SII) 1. It is considered that the detection of up regulation of transcription elongation factor A (SII) 1 comprises a third "special technical feature".
4. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of ESTs, weakly similar to KIAA0206 [H. sapiens] (GenBank Accession Number AI193075). It is considered that the detection of up regulation of ESTs, weakly similar to KIAA0206 [H. sapiens] (GenBank Accession Number AI193075) comprises a fourth "special technical feature".
5. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of human skeletal muscle 1.3 kb mRNA for tropomyosin (GenBank Accession Number AI797037). It is considered that the detection of up regulation of human skeletal muscle 1.3 kb mRNA for tropomyosin (GenBank Accession Number AI797037) comprises a fifth "special technical feature".
6. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of KIAA0701 protein (GenBank Accession Number AI797037). It is considered that the detection of up regulation of KIAA0701 protein (GenBank Accession Number AI797037) comprises a sixth "special technical feature".
7. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of mRNA for transcription elongation factor S-II, hS-II-Ti (GenBank Accession Number NM_003195). It is considered that the detection of up regulation of mRNA for transcription elongation factor S-II, hS-II-Ti (GenBank Accession Number NM_003195) comprises a seventh "special technical feature".
8. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of deafness, autosomal dominant 5 (GenBank Accession Number AF073308). It is considered that the detection of up regulation of deafness, autosomal dominant 5 (GenBank Accession Number AF073308) comprises an eighth "special technical feature".

Continued on supplemental sheet.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2003/004955

Supplemental Box

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

9. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of KIAA1037 protein (GenBank Accession Number AI383628). It is considered that the detection of up regulation of KIAA1037 protein (GenBank Accession Number AI383628) comprises a ninth "special technical feature".
10. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of KIAA0375 gene product (GenBank Accession Number AB002373). It is considered that the detection of up regulation of KIAA0375 gene product (GenBank Accession Number AB002373) comprises a tenth "special technical feature".
11. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of prefoldin 5 (GenBank Accession Number AA287397). It is considered that the detection of up regulation of prefoldin 5 (GenBank Accession Number AA287397) comprises an eleventh "special technical feature".
12. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of KIAA0710 gene product (GenBank Accession Number AB014610). It is considered that the detection of up regulation of KIAA0710 gene product (GenBank Accession Number AB014610) comprises a twelfth "special technical feature".
13. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of paired-like homeodomain transcription factor 1 (GenBank Accession Number U70370). It is considered that the detection of up regulation of paired-like homeodomain transcription factor 1 (GenBank Accession Number U70370) comprises a thirteenth "special technical feature".
14. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of retinal outer segment membrane protein 1 (GenBank Accession Number L07894). It is considered that the detection of up regulation of retinal outer segment membrane protein 1 (GenBank Accession Number L07894) comprises a fourteenth "special technical feature".
15. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of ESTs (GenBank Accession Number Z39419). It is considered that the detection of up regulation of ESTs (GenBank Accession Number Z39419) comprises a fifteenth "special technical feature".
16. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of MYC-associated zinc finger protein (purine-binding transcription factor) (GenBank Accession Number M94046). It is considered that the detection of up regulation of MYC-associated zinc finger protein (purine-binding transcription factor) (GenBank Accession Number M94046) comprises a sixteenth "special technical feature".
17. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of ubiquitin-conjugating enzyme E2L3 (GenBank Accession Number AJ000519). It is considered that the detection of up regulation of ubiquitin-conjugating enzyme E2L3 (GenBank Accession Number AJ000519) comprises a seventeenth "special technical feature".
18. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of novel human gene mapping to chromosome 1 (GenBank Accession Number AL040438). It is considered that the detection of up regulation of novel human gene mapping to chromosome 1 (GenBank Accession Number AL040438) comprises an eighteenth "special technical feature".

Continued on supplemental sheet.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2003/004955

Supplemental Box

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

19. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of Homo sapiens clone 24421 mRNA sequence (GenBank Accession Number AF07641). It is considered that the detection of up regulation of Homo sapiens clone 24421 mRNA sequence (GenBank Accession Number AF07641) comprises a nineteenth "special technical feature".
20. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of Homo sapiens mRNA; cDNA DKFZp566J2146 (GenBank Accession Number AL050081). It is considered that the detection of up regulation of Homo sapiens mRNA; cDNA DKFZp566J2146 (GenBank Accession Number AL050081) comprises a twentieth "special technical feature".
21. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of chromosome condensation 1-like (GenBank Accession Number NM_001268). It is considered that the detection of up regulation of chromosome condensation 1-like (GenBank Accession Number NM_001268) comprises a twenty-first "special technical feature".
22. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of KIAA0902 protein (GenBank Accession Number AB020709). It is considered that the detection of up regulation of KIAA0902 protein (GenBank Accession Number AB020709) comprises a twenty-second "special technical feature".
23. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of protein tyrosine kinase 9-like (A6-related protein) (GenBank Accession Number AI188660). It is considered that the detection of up regulation of protein tyrosine kinase 9-like (A6-related protein) (GenBank Accession Number AI188660) comprises a twenty-third "special technical feature".
24. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of ESTS, weakly similar to ORF YOR150w (*S. cerevisiae*) (GenBank Accession Number AI129433). It is considered that the detection of up regulation of ESTS, weakly similar to ORF YOR150w (*S. cerevisiae*) (GenBank Accession Number AI129433) comprises a twenty-fourth "special technical feature".
25. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of transcription elongation factor B (SIII), polypeptide 2 (GenBank Accession Number AW327285). It is considered that the detection of up regulation of transcription elongation factor B (SIII), polypeptide 2 (GenBank Accession Number AW327285) comprises a twenty-fifth "special technical feature".
26. Claim 19 (partially) is directed towards a method of determining liver cell cancer by detecting up regulation of cofactor required for Sp1 transcriptional activation, subunit 9 (GenBank Accession Number AA667998). It is considered that the detection of up regulation of cofactor required for Sp1 transcriptional activation, subunit 9 (GenBank Accession Number AA667998) comprises a twenty-sixth "special technical feature".
27. Claim 20 (partially) is directed towards a method of determining liver cell cancer by detecting down regulation of transmembrane protease, serine 2 (GenBank Accession Number U75329). It is considered that the detection of down regulation of transmembrane protease, serine 2 (GenBank Accession Number U75329) comprises a twenty-seventh "special technical feature".

Continued on supplemental sheet.

Supplemental Box

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

28. Claim 20 (partially) is directed towards a method of determining liver cell cancer by detecting down regulation of human gene isolated from PAC 272L16, chromosome 1, similar to calcium/calmodulin dependent protein kinase (GenBank Accession Number AL023754). It is considered that the detection of down regulation of human gene isolated from PAC 272L16, chromosome 1, similar to calcium/calmodulin dependent protein kinase (GenBank Accession Number AL023754) comprises a twenty-eighth "special technical feature".
29. Claim 20 (partially) is directed towards a method of determining liver cell cancer by detecting down regulation of CASP2 and RIPK1 domain containing adaptor with death domain (GenBank Accession Number AA811130). It is considered that the detection of down regulation of CASP2 and RIPK1 domain containing adaptor with death domain (GenBank Accession Number AA811130) comprises a twenty-ninth "special technical feature".
30. Claim 20 (partially) is directed towards a method of determining liver cell cancer by detecting down regulation of ariadne homology (GenBank Accession Number AL040708). It is considered that the detection of down regulation of ariadne homology (GenBank Accession Number AL040708) comprises a thirtieth "special technical feature".
31. Claim 20 (partially) is directed towards a method of determining liver cell cancer by detecting down regulation of NADH dehydrogenase (ubiquinone) flavoprotein 1 (GenBank Accession Number AW250734). It is considered that the detection of down regulation of NADH dehydrogenase (ubiquinone) flavoprotein 1 (GenBank Accession Number AW250734) comprises a thirty-first "special technical feature".

It is apparent from reading the specification as a whole that inventions 2-31 were derived by the applicant using an aspect of invention 1. However, the claims do not recite such a use of invention 1. Thus, since the abovementioned groups of claims do not share any of the technical features identified, a "technical relationship" between the inventions, as defined in PCT rule 13.2 does not exist. Accordingly the international application does not relate to one invention or to a single inventive concept, *a priori*.

Furthermore, inventions 2-31 are linked by the common concept of detection of up or down regulation of genes in liver cancer. However this concept is well known: see, for example, the following reviews.

Kokura K et al (1998). Gene expression in hepatomas. J Gastroenterol Hepatol. 13 Suppl: S132-41 (abstract).
Pitot HC (1996). Stage-specific gene expression during hepatocarcinogenesis in the rat. J Cancer Re Clin Oncol 122(5): 257-65 (abstract).

Thus, these inventions are not so linked as to form a single general inventive concept, that is, they do not have any common inventive features, which define a contribution over the prior art. Therefore these claims lack unity *a posteriori*.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IB2003/004955

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
WO	1999/000520	AU	81773/98
US	2002/0055099	NONE	
WO	2001/000786	AU	54234/00
		EP	1206566