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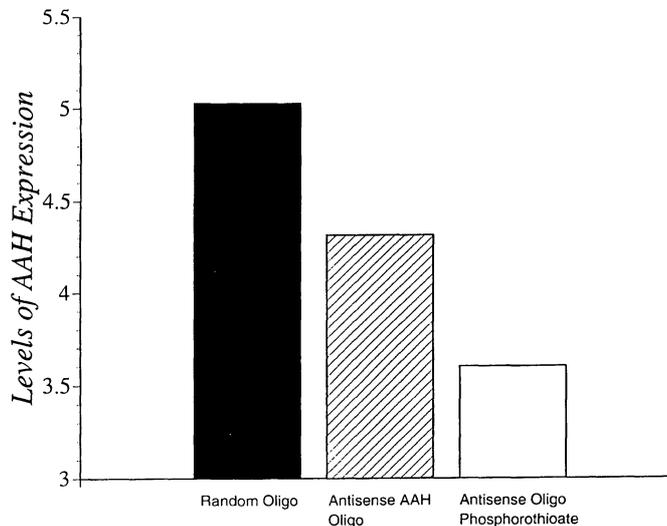
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(54) **Diagnosis and treatment of malignant neoplasms**

(57) The invention features a method for diagnosing a malignant neoplasm in a mammal by contacting a bodily fluid from the mammal with an antibody which binds to an human aspartyl (asparaginy) beta-hydroxylase

(HAAH) polypeptide and methods of treating malignant neoplasms by inhibiting HAAH. Methods of inhibiting tumor growth by contacting a tumor cell with an HAAH antisense nucleic acid are also included.

Fig 13



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European Patent  
Office

**PARTIAL EUROPEAN SEARCH REPORT**

Application Number

which under Rule 63 of the European Patent Convention EP 07 00 8309 shall be considered, for the purposes of subsequent proceedings, as the European search report

| DOCUMENTS CONSIDERED TO BE RELEVANT   |   |   |  |
|---|---|---|--|
| Category  | Citation of document with indication, where appropriate, of relevant passages   | Relevant to claim   | CLASSIFICATION OF THE APPLICATION (IPC)  |
| X   | LAVAISSIERE L ET AL: "Overexpression of human aspartyl ( asparaginyI ) beta - hydroxylase in hepatocellular carcinoma and cholangiocarcinoma."<br>JOURNAL OF CLINICAL INVESTIGATION, VOL. 98 (6) 1313-23.,<br>15 September 1996 (1996-09-15),<br>XP001004623<br>* the whole document *  | 1-3,5-9,<br>45-47   | INV.<br>G01N33/574<br>G01N33/573<br>A61K31/7088<br>A61K31/713<br>C12N15/11<br>A61K38/44<br>A61K31/44<br>A61K47/48<br>C07K16/40 |
| X   | NISHIMAKI, HIDEHARU (1) ET AL:<br>"Expression of aspartyl ( asparaginyI ) beta - hydroxylase in human gastric tissue."<br>JIKEIKAI MEDICAL JOURNAL, VOL. 46, NO. 3, PP. 129-136., September 1999 (1999-09),<br>XP001004554<br>* abstract *<br>* page 130, line 9 - line 21 *<br>* page 131, paragraph 4 - page 133 *<br>* page 134, paragraph 2 - page 135 *<br>-----<br>-/-- | 1-3,5-9,<br>45-47   | C12Q1/26<br>A61P35/00  |
|   |   |   | TECHNICAL FIELDS SEARCHED (IPC)  |
|   |   |   | G01N<br>C12Q   |
| INCOMPLETE SEARCH   |   |   |  |
| <p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:<br/>see sheet C</p> |   |   |  |
| Place of search   |   | Date of completion of the search  | Examiner   |
| The Hague   |   | 15 February 2008  | Gundlach, Björn  |
| CATEGORY OF CITED DOCUMENTS   |   | T : theory or principle underlying the invention<br>E : earlier patent document, but published on, or after the filing date<br>D : document cited in the application<br>L : document cited for other reasons<br>-----<br>& : member of the same patent family, corresponding document |  |
| X : particularly relevant if taken alone<br>Y : particularly relevant if combined with another document of the same category<br>A : technological background<br>O : non-written disclosure<br>P : intermediate document   |   |   |  |

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EPO FORM 1503 03/02 (P04E07)



| DOCUMENTS CONSIDERED TO BE RELEVANT |   |                   | CLASSIFICATION OF THE APPLICATION (IPC) |
|-------------------------------------|---|-------------------|---|
| Category                            | Citation of document with indication, where appropriate, of relevant passages   | Relevant to claim |   |
| X                                   | NISHIMAKI, H. (1) ET AL: "Cellular overexpression of human asparaginyl / aspartyl beta- hydroxylase (HAAH) in gastric and colon cancers."<br>GASTROENTEROLOGY, VOL. 112, NO. 4 SUPPL., PP. A628. MEETING INFO.: DIGESTIVE DISEASE WEEK AND THE 97TH ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION WASHINGTON, D.C., USA MAY 11-14, 1997, 1997, XP001004543<br>* abstract * | 1-3,5-9,<br>45-47 |   |
| X                                   | INCE, N. (1) ET AL: "Overexpression of HAAH (human aspartyl, asparaginyl hydroxylase ) in bile ducts is related to malignant transformation"<br>HEPATOLOGY, VOL. 26, NO. 4 PART 2, PP. 362A. MEETING INFO.: 48TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES CHICAGO, ILLINOIS, USA NOVEMBER 7-11, 1997, 1997, XP001004629<br>* abstract *                   | 1-3,5-9,<br>45-47 | TECHNICAL FIELDS SEARCHED (IPC)         |
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| DOCUMENTS CONSIDERED TO BE RELEVANT |  |                   | CLASSIFICATION OF THE APPLICATION (IPC) |
|-------------------------------------|--|-------------------|---|
| Category                            | Citation of document with indication, where appropriate, of relevant passages  | Relevant to claim |   |
| P,X                                 | INCE N ET AL: "Overexpression of human aspartyl ( asparaginy) beta - hydroxylase is associated with malignant transformation."<br>CANCER RESEARCH, 60 (5) 1261-6.,<br>March 2000 (2000-03), XP001002102<br>* the whole document *  | 1-3,5-9,<br>45-47 |   |
| X                                   | KORIOTH F ET AL: "Cloning and characterization of the human gene encoding aspartyl beta-hydroxylase"<br>GENE, ELSEVIER, AMSTERDAM, NL,<br>vol. 150, no. 2,<br>15 December 1994 (1994-12-15), pages<br>395-399, XP002109354<br>ISSN: 0378-1119<br>* abstract *<br>-& DATABASE EMBL [Online]<br>8 March 1994 (1994-03-08), "Human aspartyl beta-hydroxylase mRNA, complete cds."<br>XP002469165<br>Database accession no. U03109<br>* abstract * | 21-26             | TECHNICAL FIELDS<br>SEARCHED (IPC)      |
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| X                                   | WO 99/30562 A (CORNELL RES FOUNDATION INC [US]) 24 June 1999 (1999-06-24)<br>* figure 1 *<br>* claims 1-6 *  | 27-38             |   |
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| DOCUMENTS CONSIDERED TO BE RELEVANT |   |                   | CLASSIFICATION OF THE APPLICATION (IPC) |
|-------------------------------------|---|-------------------|---|
| Category                            | Citation of document with indication, where appropriate, of relevant passages   | Relevant to claim |   |
| X                                   | INCE N ET AL: "THE INSULIN RECEPTOR SUBSTRATE-1 (HIRS-1) SIGNAL TRANSDUCTION PATHWAY INFLUENCES EXPRESSION OF HUMAN ASPARTYL (ASPARAGINYL) BETA-HYDROXYLASE (HAAH) IN HUMAN HEPATO-CELLULAR CARCINOMA CELLS"<br>HEPATOLOGY, WILLIAMS AND WILKINS, BALTIMORE, MD, US,<br>vol. 30, no. 4, October 1999 (1999-10), page 510A, XP001004541<br>ISSN: 0270-9139<br>* abstract * | 10-26             |   |
| A                                   | -----<br>WO 99/47683 A (RADOSEVICH JAMES A [US])<br>23 September 1999 (1999-09-23)<br>* the whole document *<br>-----   | 10-26             | TECHNICAL FIELDS SEARCHED (IPC)         |
|                                     |   |                   |   |



Claims 1-9 are directed to a diagnostic method practised on the human/animal body (Article 53(c) EPC), the search has been carried out in as far as ex vivo methods are concerned.  
Although claims 10-20 and 27-39 are directed to a method of treatment of the human/animal body (Article 53(c) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

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Claim(s) searched completely:  
45-47

Claim(s) searched incompletely:  
1-20,27-39

Reason for the limitation of the search (non-patentable invention(s)):

Article 53 (c) EPC - Diagnostic method practised on the human or animal body

Article 53 (c) EPC - Method for treatment of the human or animal body by therapy

**CLAIMS INCURRING FEES**

The present European patent application comprised at the time of filing more than ten claims.

- Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

**LACK OF UNITY OF INVENTION**

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:  
1-47 (groups of inventions 1 and 2)
- None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:
- The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).



The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-9,45-47

Method for diagnosing malignant neoplasms with antibodies

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2. claims: 10-44

Method of inhibiting tumor growth in a mammal using a  
compound which inhibits the expression of HAAH

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3. claims: 48,49

Methods of determining whether candidate compounds inhibit  
HAAH

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**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 07 00 8309

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-02-2008

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

|                |  |         |            |
|----------------|--|---------|------------|
| 专利名称(译)        | 恶性肿瘤的诊断和治疗   |         |            |
| 公开(公告)号        | <a href="#">EP1881327A3</a>  | 公开(公告)日 | 2008-04-02 |
| 申请号            | EP2007008309   | 申请日     | 2000-11-08 |
| [标]申请(专利权)人(译) | 罗德岛医院  |         |            |
| 申请(专利权)人(译)    | 罗德岛医院  |         |            |
| 当前申请(专利权)人(译)  | 罗德岛医院  |         |            |
| [标]发明人         | WANDS JACK R<br>CARLSON ROLF I<br>DE LA MONTE SUZANNE M<br>INCE M NEDIM  |         |            |
| 发明人            | WANDS, JACK R.<br>CARLSON, ROLF I.<br>DE LA MONTE, SUZANNE M.<br>INCE, M. NEDIM  |         |            |
| IPC分类号         | G01N33/574 G01N33/573 A61K31/7088 A61K31/713 C12N15/11 A61K38/44 A61K31/44 A61K47/48<br>C07K16/40 C12Q1/26 A61P35/00 A61K31/00 A61K31/4412 A61K31/45 A61K38/43 A61K39/395<br>A61K45/00 A61K48/00 C07K14/47 C12N9/02 C12N15/09 C12N15/113 C12P21/08 C12Q1/02 G01N33<br>/53 G01N33/577 |         |            |
| CPC分类号         | C12N15/1137 A61K31/00 A61K31/4412 A61K2039/505 C07K14/47 C07K16/40 C12N9/0071 C12N2310<br>/111 C12N2310/315 C12N2799/027 C12Q1/26 C12Y114/11016 G01N33/574 G01N33/57484<br>G01N2500/00 G01N2500/10   |         |            |
| 优先权            | 09/436184 1999-11-08 US  |         |            |
| 其他公开文献         | EP1881327A2  |         |            |
| 外部链接           | <a href="#">Espacenet</a>  |         |            |

摘要(译)

本发明的特征在于一种通过使来自哺乳动物的体液与结合人天冬氨酰(天冬酰胺酰)β-羟化酶(HAAH)多肽的抗体接触以及通过抑制HAAH治疗恶性肿瘤的方法来诊断哺乳动物的恶性肿瘤的方法。还包括通过使肿瘤细胞与HAAH反义核酸接触来抑制肿瘤生长的方法。

