Title: USE OF NRG4, OR INHIBITORS THEREOF, IN THE TREATMENT OF COLON AND PANCREATIC CANCER

Abstract: This invention relates to compositions and uses of NRG4, and to variants thereof and to polynucleotides encoding NRG4, for therapeutic and diagnostic purposes, particularly related to colon and pancreatic cancer. This invention also relates to therapeutic agents based on or derived from the polynucleotides and proteins, NRG4 inhibitors, particularly antibodies capable of specifically binding to NRG4.
A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12Q 1/68; C07H 21/04; C07K 14/00
US CL. : 435/6; 536/23.1; 530/350
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)
U.S. : C12Q 1/68; C07H 21/04; C07K 14/00

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 practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>HARARI D, et al. Neuregulin-4: a novel growth factor that acts through the ErbB-4 receptor tyrosine kinase. Oncogene. 1999, Vol. 18, pages 2681-2689; see entire</td>
<td>1, 2, and 5-7</td>
</tr>
<tr>
<td>Y,P</td>
<td>US 2004/0005622 A1 (SCHLEYER et al.) 08 January 2004 (08.01.2004); see entire document, particularly page 13, Example 1.</td>
<td>1, 2, and 5-7</td>
</tr>
<tr>
<td>Y,P</td>
<td>US 6,544,759 B1 (HARARI et al.) 08 April 2003 (08.04.2003); see entire document.</td>
<td>1, 2, and 5-7</td>
</tr>
<tr>
<td>Y</td>
<td>WO 01/81540 A2 (YEDA RESEARCH AND DEVELOPMENT CO. LTD.) 01 November 2001 (01.11.2001); see entire document, e.g., claims 63 and 64.</td>
<td>1, 2, and 5-7</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search: 29 September 2004 (29.09.2004)

Date of mailing of the international search report: 21 OCT 2004

Authorized officer: Stephen L. Rawlings, Ph.D.
Telephone No.: (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)
BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1, 2, and 5-7, drawn to a method for diagnosing colon cancer or pancreatic cancer comprising determining an amount of a mRNA molecule encoding NRG4.

Group II, claim(s) claims 3 and 4, drawn to a method for diagnosing an NRG4-modulated disorder comprising determining an amount of NRG4 polypeptide.

Group III, claim(s) 8, insofar as the claim is drawn to a method for modulating the amount of NRG4 in a subject comprising administering a polynucleotide encoding NRG4.

Group IV, claim(s) 8, insofar as the claim is drawn to a method for modulating the amount of NRG4 in a subject comprising administering an NRG4 polypeptide.

Group V, claim(s) 8 and 10-14, insofar as the claim is drawn to a method for modulating the amount of NRG4 in a subject comprising administering an antibody that binds NRG4.

Group VI, claim(s) 9, insofar as the claim is drawn to a method for treating a NRG4-modulated disorder comprising administering an antisense construct.

Group VII, claim(s) 9, insofar as the claim is drawn to a method for treating a NRG4-modulated disorder comprising administering a ribozyme.

Group VIII, claim(s) 9, insofar as the claim is drawn to a method for treating a NRG4-modulated disorder comprising administering an RNAi.

Group IX, claim(s) 15-18, drawn to a method inhibiting the expression of an NRG4 target gene in a cell in vitro comprising introducing a double-stranded RNA molecule into a cell.

Group X, claim(s) 19-22, drawn to a method for inhibiting the expression of an NRG4 gene in an organism comprising providing an organism having a target cell and contacting the organism with a double-stranded RNA molecule.

The inventions listed as Groups I-X do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of group I is determining an amount of a mRNA molecule encoding NRG4.

The special technical feature of group II is determining an amount of NRG4 polypeptide.

The special technical feature of group III is administering a polynucleotide encoding NRG4.

The special technical feature of group IV is administering an NRG4 polypeptide.

The special technical feature of group V is administering an antibody that binds NRG4.

The special technical feature of group VI is administering an antisense construct.

The special technical feature of group VII is administering a ribozyme.
The special technical feature of group VIII is administering an RNAi.

The special technical feature of group IX introducing a double-stranded RNA molecule into a cell \textit{in vitro}.

The special technical feature of group X is providing an organism having a target cell and contacting the organism with a double-stranded RNA molecule.

Accordingly, groups I-X do not share the same or corresponding special technical feature so as to form a single general inventive concept under PCT Rules 13.1 and 13.2. In addition, PCT Rules 13.1 and 13.2 do not provide for a single general inventive concept to comprise more than the first mentioned product, the first mentioned method for making said product, and the first mentioned method for using said product.

\textbf{Continuation of B. FIELDS SEARCHED Item 3:}

\textsc{WEST, MEDLINE}: herregulin-4 (HRG4); cancer; pancreatic; colon; diagnosis; overexpression; Northern; differential expression
INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claim Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. ✗ Claim Nos.: 23 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: Claim 23 was found unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a).

3. □ Claim 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:

Please See Continuation 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, 2 and 5-7

Remark on Protest □ The additional search fees were accompanied by the applicant's protest.

□ No protest accompanied the payment of additional search fees.