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(54) Title: CRYSTAL STRUCTURES OF NEUROPLIN FRAGMENTS AND NEUROPLIN-ANTIBODY COMPLEXES

(57) Abstract: The invention provides crystal structures of neuropilin 1 (Nrp1) and neuropilin 2 (Nrp2) fragments alone and in complex with anti-neuropilin antibodies, and method for their use. The invention further provides anti-Nrp antibodies and methods for their therapeutic applications.
### Classification of Subject Matter

**INV. C07K14/71**

According to International Patent Classification (IPC) or to both national classification and IPC

### Fields Searched

**C07K G06F**

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEMABS Data, EMBASE, WPI Data, PAJ

### 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>
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<tbody>
<tr>
<td>X</td>
<td>&amp; DATABASE PDB [Online] retrieved from <a href="HTTP://WWW.PDB.ORG/PDB/EXPLORE.DOC?STRUCTURE=EID=20RX">HTTP://WWW.PDB.ORG/PDB/EXPLORE.DOC?STRUCTURE=EID=20RX</a> Database accession no. 2orx the whole document</td>
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</table>

Further documents are listed in the continuation of Box C.

See patent family 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 claims or which is cited to establish the publication date of another citation or other special reason (as specified)
  * **C** document referring to an oral disclosure, use, exhibition or other means
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  * **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
  * **A** document member of the same patent family

Date of the actual completion of the international search: 2 December 2008

Date of mailing of the international search report: 15/12/2008

Name and mailing address of the ISA/European Patent Office, P.B. 5016 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer: Seranski, Peter
<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>
</table>
| P,X      | APPLETON BRENT A ET AL: "Structural studies of neuropilin/antibody complexes provide insights into semaphorin and VEGF binding."  
           ISSN: 1460-2075  
           the whole document                                                                                                             | 1-39                 |
| P,X      | GERETTI ELENA ET AL: "Neuropilin structure governs VEGF and semaphorin binding and regulates angiogenesis."  
           ISSN: 0969-6970  
           the whole document                                                                                                             | 7-23                 |
| A        | LEE CHRISTIAN C ET AL: "Crystal structure of the human neuropilin-1 bi-domain."  
           ISSN: 0969-2126                                                                                                                  | 2,3                  |
| A        | PAN QI ET AL: "Blocking neuropilin-1 function has an additive effect with anti-VEGF to inhibit tumor growth."  
           ISSN: 1535-6108                                                                                                                 | 6-39                 |
| A        | LIANG ET AL: "Function Blocking Antibodies to Neurupilin-1 Generated from a Designed Human Synthetic Antibody Phage Library"  
           ISSN: 0022-2836                                                                                                                 | 8-30                 |
| A        | GIGER R J ET AL: "Neuropilin-2 is a receptor for semaphorin IV: insight into the structural basis of receptor function and specificity."  
           ISSN: 0896-6273                                                                                                                 | 4-30                 |
Continuation of Box II.1

Although claims 40-48 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 40-48

The present claim 40-48 relate to an extremely large number of possible compounds. No support and disclosure in the sense of Article 6 and 5 PCT is to be found in the whole application for at least one such compound. The non-compliance with the substantive provisions is to such an extent, that no search was performed. (PCT Guidelines 9.19 and 9.23).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2) PCT declaration be overcome.
### INTERNATIONAL SEARCH REPORT

**Box No. II**  Observations where certain claims were found unsearchable (Continuation of Item 2 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. **X** Claims Nos.:  
   because they relate to subject matter not required to be searched by this Authority, namely:
   
   Although claims 40-48 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **X** Claims Nos.: 40-48  
   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:
   
   see FURTHER INFORMATION sheet PCT/ISA/210.

3. **☐** Claims Nos.:  
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 5.4(a).

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**Box No. III**  Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- see additional sheet

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1. **X** 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 additional fees.

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 and, where applicable, the payment of a protest fee.
- **☐** The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- **X** No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claim: 1

Crystal formed by an Nrp1(b1b2) fragment with the Space Group P2(1)2(1)2(1).

2. claim: 2

Crystal formed by an Nrp1(a2b1b2) fragment with the Space Group P2(1).

3. claims: 3, 31-39

Crystal of a complex formed between Nrp1(b1) fragment and a Fab fragment of anti-Nrp1(B) antibody with Space group H3; Method of preparing a VEGF antagonist using said crystal structure; Method of treatment cancer using said antagonist.

4. claim: 4

Crystal formed by an Nrp2(b1b2) fragment with the Space Group P2(1)2(1)2(1).

5. claim: 5

Crystal formed by an Nrp2(a2b1b2) fragment with the Space Group P2(1).

6. claims: 6-30

Crystal of a complex between Nrp2(ala2B1B2) fragment and a Fab fragment of anti-panNrp(A) antibody with space group of C2; Crystal of a complex between Nrp2(ala2B1B2) fragment and a Fab fragment of anti-panNrp(A) antibody with space group of P3(2)21; anti-panNrp(A) antibody comprising light chain variable domain of Fig.7 and/or heavy chain variable domain sequence shown in Fig 8 or fragment thereof; anti-panNrp(A) antibody Fab fragment with Sequence shown in Fig.9B; Anti-Nrp antibody that competes for Nrp binding with anti-panNrp(A) antibody; Method for preparing semaphorin antagonist which blocks semaphorin binding to Nrp1 and Nrp2