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AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

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**Declaration under Rule 4.17:**

— of inventorship (Rule 4.17(iv))

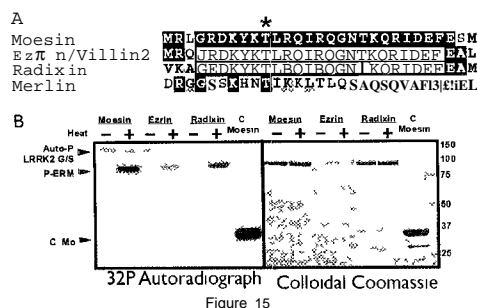
**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:  
4 December 2008

(54) Title: METHODS FOR MODULATING LRRK2

LRRK2 phosphorylates Ezrin and Radixin



(57) Abstract: A method for identifying a compound expected to be useful in modulating a LRRK2 protein kinase activity, the method comprising the steps of (1) determining whether a test compound modulates the protein kinase activity of a LRRK2 polypeptide on a substrate Ezrin/Radixin/moesin (ERM) family polypeptide and (2) selecting a compound which modulates the LRRK2 polypeptide protein kinase activity. Such a compound may be useful in treating Parkinson's Disease or Parkinsonism. A catalytically active fragment of LRRK2 is identified, requiring the GTPase, COR and kinase domains as well as the WD<sub>40</sub>-like motif and C-terminal tail.

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**INTERNATIONAL SEARCH REPORT**

International application No  
**PCT/GB2008/001211**

**A. CLASSIFICATION OF SUBJECT MATTER**  
**INV. C12Q1/48 C07K14/00**

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)  
**C12Q C07K**

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 , BIOSIS, Sequence Search, EMBASE, COMPENDEX, INSPEC, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
<b>X</b>	US 2003/166222 A1 (MEYERS RACHEL E [US]) 4 September 2003 (2003-09-04) sequence 2	24, 25, 28
<b>X</b>	US 2004/265849 A1 (CARGILL MICHELE [US] ET AL) 30 December 2004 (2004-12-30) sequence 815	24, 25, 28
<b>X</b>	WO 2004/074485 A (RES ASS FOR BIOTECHNOLOGY [JP]; ZOEGENE CORP [JP]; ISOGAI TAKAO [JP];) 2 September 2004 (2004-09-02) sequence 21	24, 28
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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 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

Date of the actual completion of the international search	Date of mailing of the international search report
9 September 2008	25/09/2008

Name and mailing address of the ISA/ European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer  <b>Jacques , Patrice</b>
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2008/001211

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category <sup>1</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KATAYAMA S ET AL: "Anti sense transcription in the mammalian transcriptome" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, US; WASHINGTON, DC, vol. 309, no. 5740, 2 September 2005 (2005-09-02), pages 1564-1566, XP003020135 ISSN: 0036-8075 the whole document -&amp; DATABASE UniProt [Online] 11 October 2005 (2005-10-11), "SubName: Full=Putative uncharacterized protein; Flags: Fragment;" XP002494863 retrieved from EBI accession no. UNIPROT:Q3UF33 Database accession no. Q3UF33</p>	27,29
P,X	<p>JALEEL MAHABOBI ET AL: "LRRK2 phosphorylates moesin at threonine-558: characterization of how Parkinson's disease mutants affect kinase activity" BIOCHEMICAL JOURNAL, vol. 405, no. Part 2, July 2007 (2007-07), pages 307-317, XP002494862 ISSN: 0264-6021(print) 1470-8728(ele the whole document</p>	1-34,37
A	<p>MATSUI T ET AL: "RHO-KINASE PHOSPHORYLATES COOH-TERMINAL THREONINES OF EZRIN/RADIXIN/MOESIN (ERM) PROTEINS AND REGULATES THEIR HEAD-TO-TAIL ASSOCIATION" THE JOURNAL OF CELL BIOLOGY, ROCKEFELLER UNIVERSITY PRESS, US, vol. 140, no. 3, 9 February 1998 (1998-02-09), pages 647-657, XP001083757 ISSN: 0021-9525 the whole document</p>	3
A	<p>MATA ET AL: "LRRK2 in Parkinson's disease: protein domains and functional insights" TRENDS IN NEUROSCIENCE, ELSEVIER, AMSTERDAM, NL, vol. 29, no. 5, 1 May 2006 (2006-05-01), pages 286-293, XP005415125 ISSN: 0166-2236 the whole document</p>	1-34,37

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 35 (fully), 36 (fully)

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Continuation of Box II.2

Claims Nos.: 35-36

The subject-matter of claims 35 and 36 represents an attempt to gain protection for the product. The said claims represent a combination of two different and irreconcilable types of process claims, namely (i) the use of the compound to achieve a technical effect and (ii) a process for the production of a product. Step 2) of claim 36 and claim 35 builds on the "effect" achieved by the previous step, rather than feeding into said step 2) a specific material and resulting in a specific product. This results in an unclear claim according to Art. 6 PCT.

The said claims thus encompass compounds defined only by their desired function, contrary to the requirements of clarity of Article 6 PCT, because the result-to-be-achieved type of definition does not allow the scope of the claim to be ascertained. The fact that any compound could be screened does not overcome this objection, as the skilled person would not have knowledge beforehand as to whether it would fall within the scope claimed. Undue experimentation would be required to screen compounds randomly. This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search for claims 35 and 36.

As no compounds are defined in the description, the said claims have not been searched.

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

International application No.  
PCT/GB2008/001211

## 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.  Claims Nos.: 35 (fully), 36 (fully)  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: 35-36  
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 6.4(a)

## 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:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable **claims.**
  
2.  As all searchable claims could be searched without effort justifying an additional fees, 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.
- No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2008/001211

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
<b>US</b> 2003166222	<b>A1</b>	04-09-2003	<b>NONE</b>	
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<b>us</b> 2004265849	<b>A1</b>	30-12-2004	<b>NONE</b>	
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<b>UO</b> 2004074485	<b>A</b>	02-09-2004	<b>JP</b> 2006174701 <b>A</b>	06-07-2006
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