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Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(U))*

Published:
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— *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:
18 September 2008

(54) Title: INHIBITION OF GPR4

(57) Abstract: The present invention relates to the use of a GPR4 inhibitor for the manufacture of a medicament for the inhibition of angiogenesis, for instance for the inhibition of tumour growth in the treatment of cancer. In a preferred embodiment, said inhibitor is a siRNA, preferably double-stranded. In addition, the present invention further encompasses non-human animals wherein the GPR4 has been inactivated, for instance a knock-out mouse lacking GPR4, and the use of said animals as an experimental model for angiogenesis and for screening for compounds modulating angiogenesis.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/063899

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/11 **A61K48/00** **A01K67/027**

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)
C12N

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, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Cftation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/112823 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; BAUMSARTEN, BIRGIT [DE]; J) 29 December 2004 (2004-12-29) page 5, last paragraph - page 6, paragraph 2 page 40 - page 56; examples 8-25 claims 1-15 ----- -/-	1-5,8,9

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents

[1]A* document defining the general slate 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[1] document which may throw doubts on priority claim(s) or which is cried 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

[1]P[1] document published prior to the international filing date but later than the priority date claimed

[1]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 ortheory 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[1] 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 docu¬ments, 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
22 April 2008	17/07/2008

Name and mailing address of the ISA/	Authonzed officer
European Patent Office, P B. 5818 Patentlaan 2 NL ¬ 2280 HV Rijswl|k Tel (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Dumont , El i sabeth

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/063899

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category"	Citation of document, with indication where appropriate of the relevant passages	Relevant to claim No
X	KIM KWAN-SIK ET AL: "GPR4 plays a critical role in endothelial cell function and mediates the effects of sphingosyl phosphoryl choline." THE FASEB JOURNAL : OFFICIAL PUBLICATION OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY MAY 2005, vol. 19, no. 7, May 2005 (2005-05), pages 819-821, XP002420334 ISSN: 1530-6860 The whole document, in particular page 819, column 2, paragraph 1 page 821, 'Conclusions'	1-5,8,9
X	WO 03/033661 A2 (MILLENNIUM PHARM INC [US]; LOGAN THOMAS JOSEPH [US]; GALVIN KATHERINE) 24 April 2003 (2003-04-24) page 2, line 11 - page 9, line 5 claims 1-6	1-5,8,9
X	XU Y. ET AL: "GPR4 PLAYS A CRITICAL ROLE IN THE SURVIVAL, PROLIFERATION, AND DIFFERENTIATION OF ENDOTHELIAL CELLS (Abstract 5)" CLEVELAND CLINIC JOURNAL OF MEDICINE, ABSTRACTS FROM THE FIRST ANNUAL ATHEROTHROMBOSIS SUMMIT (17-19 SEPTEMBER 2003) CLEVELAND, OHIO, [Online] vol. 70, no. E-SUPPLEMENT1, September 2003 (2003-09), pages ES-l-ES-7, XP002420345 Retrieved from the Internet: URL:http://www. ccjm.org/PDFFILES/ATSummitabstracts .pdf#Abstract4and5> [retrieved on 2007-02-15] abstract	1-5,8,9
X	SEUWEN KLAUS ET AL: "REVIEW - RECEPTORS FOR PROTONS OR LIPID MESSENGERS OR BOTH?" JOURNAL OF RECEPTOR AND SIGNAL TRANSDUCTION RESEARCH, MARCEL DEKKER, NEW YORK, NY, US, vol. 26, no. 5-6, September 2006 (2006-09), pages 599-610, XP009078956 ISSN: 1079-9893 the whole document	1-5,8,9
X	WO 03/096025 A (BAYER AG [DE]; GOLZ STEFAN [DE]; BRUEGGEMEIER ULF [DE]; SUMMER HOLGER) 20 November 2003 (2003-11-20) page 38 page 55 - page 56	1-5,8,9

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/063899

C(Contlnuatlon) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Ctation of document, with indication, where appropriate of the relevant passages	Relevant to claim No
A	WO 2005/059132 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; HALL JONATHAN [CH]; HUESK) 30 June 2005 (2005-06-30) cited in the application the whole document	1-5,8,9

INTERNATIONAL SEARCH REPORT

International application No
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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:

see FURTHER INFORMATION sheet PCT/lSA/210

2. [X] Claims Nos :
because they relate to parts of the international application that do not comply with trie 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 Rjle 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:

see additional sheet

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 reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [Y] 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..

1-4, **8, 9 (partially), 5 (completely)**

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 tees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions 1n this international application, as follows:

1. claims: 1-4, 8, 9 (partially), claim 5 (completely)

Subject-matter relating to an siRNA molecule comprising the sequence of SEQ ID NO: 1 (sense) or 2 (anti sense), its use 1n treatment or for the manufacture of a medicament for the inhibition of angiogenesis

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2. claims: 1-4, 8, 9 (partially), claim 6 (completely)

As invention 1, with an siRNA molecule comprising the sequence of SEQ ID NO: 4 (sense) or 5 (anti sense)

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3. claims: 1-4, 8, 9 (partially), claim 7 (completely)

As invention 1, with an siRNA molecule comprising the sequence of SEQ ID NO: 7 (sense) or 8 (anti sense)

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4. claims: 1-4, 8, 9 (partially)

As Invention 1, with an s1RNA molecule comprising the sequence of SEQ ID NO: 10 (sense) or 11 (antisense)

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5. claims: 1-4, 8, 9 (partially)

As invention 1, with an siRNA molecule comprising the sequence of SEQ ID NO: 13 (sense) or 14 (antisense)

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6. claims: 1-4, 8, 9 (partially)

As invention 1, with an siRNA molecule comprising the sequence of SEQ ID NO: 16

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7. claims: 1-4, 8, 9 (partially)

As invention 1, with an siRNA molecule comprising the sequence of SEQ ID NO: 17

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8. claims: 1-4, 8, 9 (partially)

As invention 1, with an s1RNA molecule comprising the sequence of SEQ ID NO: 18

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9. claims: 1-4, 8, 9 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

As invention 1, with an siRNA molecule comprising the sequence of SEQ ID NO: 19

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10. claims: 1-4, 8, 9 (partially)

As invention 1, with an siRNA molecule comprising the sequence of SEQ ID NO: 20

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11. claims: 10-12

Subject-matter relating to a non human animal wherein the gene coding for GPR4 has been deleted; its use as an experimental model for angiogenesis and in screening

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12. claim: 13

Subject-matter relating to a method for identifying an inhibitor of GPR4

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claim 8 is 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.1

Claims Nos. : -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box II.2

Claims Nos. : -

The present claims 1, 2 and 8 encompass compounds defined only by their desired function (GPR4 inhibition), 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, except for the siRNA molecules disclosed in the description, see pages 12 and 13. 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 1, 2 and 8.

The search of claims 1, 2 and 8 was consequently restricted to the use of siRNA according to invention 1.

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

Information on patent family members

International application No
PCT/EP2007/063899

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