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- (71) Applicant: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; 124 Grenzacherstrasse, CH-4070 Basle (CH).
- (72) Inventors: **BRANDT, Michael**; Faltergatter 29, 82393 Ifeldorf (DE). **BROCKMANN, Marc**; Glockengiesserstr. 87, 23552 Luebeck (DE). **LAMSZUS, Katrin**; Am Ree 52a, 22459 Hamburg (DE). **PAPADIMITRIOU, Apollon**; Bachstrasse 38a, 83673 Bichl (DE). **SCHUELL, Christine**; Waldst. 1, 82377 Penzberg (DE).
- (74) Agent: **SCHREINER, Siegfried**; Roche Diagnostics GmbH, Patent Department (TR-E), P.O. Box 11 52, 82372 Penzberg (DE).
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- (88) Date of publication of the international search report: 15 April 2004
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(54) Title: SCATTER FACTOR/HEPATOCYTE GROWTH FACTOR ANTAGONIST NK4 FOR THE TREATMENT OF GLIOMA

(57) Abstract: A pharmaceutical composition for the treatment of a tumor derived from glia cells of the central nervous system (CNS) of a patient, characterized in that the composition contains a pharmaceutically effective amount of a fragment of the hepatocyte growth factor, said fragment consisting of the N-terminal hairpin domain and the four kringle domains of the hepatocyte growth factor alfa-chain. (NK4).



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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/09545

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/48 A61P35/00 A61K38/18

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)

IPC 7 A61K

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, PAJ, WPI Data, MEDLINE, CANCERLIT, DISSERTATION ABS, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 234 583 A (HOFFMANN LA ROCHE) 28 August 2002 (2002-08-28) examples claims	1-6
Y	----- GUERIN CHRISTOPHER ET AL: "Glioma inhibition by HGF/NK2, an antagonist of scatter factor/hepatocyte growth factor." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 273, no. 1, 24 June 2000 (2000-06-24), pages 287-293, XP002249671 ISSN: 0006-291X abstract tables 1-3 figures 2-4 ----- -/--	1-6

Further documents are listed in the continuation of box C.

Patent family members are listed in 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
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- *&* document member of the same patent family

Date of the actual completion of the international search

20 February 2004

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01/03/2004

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

Dullaart, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/09545

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>ARRIETA OSCAR ET AL: "Hepatocyte growth factor is associated with poor prognosis of malignant gliomas and is a predictor for recurrence of meningioma." CANCER, vol. 94, no. 12, 15 June 2002 (2002-06-15), pages 3210-3218, XP002249672 ISSN: 0008-543X abstract figure 1 page 3214, right-hand column, last paragraph - page 3216, left-hand column, last line</p>	1-6
Y	<p>ABOUNADER ROGER ET AL: "In vivo targeting of SF/HGF and c-met expression via U1snRNA/ribozymes inhibits glioma growth and angiogenesis and promotes apoptosis." FASEB JOURNAL, vol. 16, no. 1, January 2002 (2002-01), pages 108-110, XP002249673 January, 2002 ISSN: 0892-6638 * page 108, left-hand column, paragraph SPECIFIC AIMS * page 110, paragraph CONCLUSIONS</p>	1-6
Y	<p>LAMSZUS KATRIN ET AL: "Scatter factor/hepatocyte growth factor (SF/HGF) content and function in human gliomas." INTERNATIONAL JOURNAL OF DEVELOPMENTAL NEUROSCIENCE, vol. 17, no. 5-6, August 1999 (1999-08), pages 517-530, XP002249674 ISSN: 0736-5748 abstract tables 1-5 page 525, last paragraph - page 528, paragraph CONCLUSIONS</p>	1-6
Y	<p>DATE K ET AL: "HGF/NK4 IS A SPECIFIC ANTAGONIST FOR PLEIOTROPHIC ACTIONS OF HEPATOCYTE GROWTH FACTOR" FEBS LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 420, no. 1, 1997, pages 1-6, XP002920323 ISSN: 0014-5793 abstract figures 1-3 page 5, paragraph DISCUSSION - page 6</p>	1-6

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/09545

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DATE K ET AL: "INHIBITION OF TUMOR GROWTH AND INVASION BY A FOUR-KRINGLE ANTAGONIST (HGF/NK4) FOR HEPATOCYTE GROWTH FACTOR" ONCOGENE, BASINGSTOKE, HANTS, GB, vol. 17, no. 23, 1998, pages 3045-3054, XP001008680 ISSN: 0950-9232 page 3049, right-hand column, last paragraph - page 3051, left-hand column, line 5</p>	1-6
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Y	<p>WO 94/13322 A (MARCUCCI FABRIZIO ;ERBA CARLO SPA (IT); GREGORY RUTH (IT)) 23 June 1994 (1994-06-23) page 8 claims</p>	1-6
Y	<p>FRANCIS G E ET AL: "PEGylation of cytokines and other therapeutic proteins and peptides: The importance of biological optimisation of coupling techniques." INTERNATIONAL JOURNAL OF HEMATOLOGY, vol. 68, no. 1, July 1998 (1998-07), pages 1-18, XP001010042 ISSN: 0925-5710 abstract page 2 page 6, paragraph 4.1 page 7 page 10, paragraph 4.2 - page 12, right-hand column, line 2 page 13, left-hand column, last line - page 15, left-hand column, line 2 figure 1</p>	1-6

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/09545

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>TSUTSUMI YASUO ET AL: "PEGylation of interleukin-6 effectively increases its thrombopoietic potency." THROMBOSIS AND HAEMOSTASIS, vol. 77, no. 1, 1997, pages 168-173, XP001010032 ISSN: 0340-6245 abstract</p>	1-6
Y	<p>-----</p> <p>TSUTSUMI YASUO ET AL: "Site-specific chemical modification with polyethylene glycol of recombinant immunotoxin anti-Tac(Fv)-PE38 (LMB-2) improves antitumor activity and reduces animal toxicity and immunogenicity." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 97, no. 15, 18 July 2000 (2000-07-18), pages 8548-8553, XP002175033 July 18, 2000 ISSN: 0027-8424 abstract page 8551, left-hand column, last paragraph - right-hand column, line 5; table 3</p>	1-6
Y	<p>-----</p> <p>REDDY K RAJENDER: "Controlled-release, pegylation, liposomal formulations: New mechanisms in the delivery of injectable drugs." ANNALS OF PHARMACOTHERAPY, vol. 34, no. 7-8, July 2000 (2000-07), pages 915-923, XP001010043 ISSN: 1060-0280 abstract table 1 page 919, left-hand column, paragraph - page 921, right-hand column</p>	1-6
Y	<p>-----</p> <p>WO 01/44294 A (DEY CLARA ; SIM KIM LEE (US); ENTREMED INC (US); LIANG HONG (US)) 21 June 2001 (2001-06-21) the whole document</p>	1,3,5
Y	<p>-----</p> <p>EP 1 074 264 A (NAKAMURA TOSHIKAZU) 7 February 2001 (2001-02-07) examples tables</p> <p>-----</p>	1,3,5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/09545

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5-6 are directed to a method of treatment of the human/animal body, a search has been carried out, based on the alleged effects of the compound/composition.
2. Claims Nos.:
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:
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 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:

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.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/09545

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