(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 March 2001 (01.03.2001)

PCT

(10) International Publication Number
WO 01/14420 A3

(51) International Patent Classification[7]: C12N 15/12, 15/62, 15/63, C07K 14/705, 16/28, C12P 21/02, A61K 38/17, 39/395, G01N 33/53

(21) International Application Number: PCT/US00/23365

(22) International Filing Date: 25 August 2000 (25.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/150,576 25 August 1999 (25.08.1999) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
10 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/14420 A3

(54) Title: NOVEL MEMBERS OF THE PLEXIN FAMILY AND USES THEREOF

(57) Abstract: The invention provides methods and compositions related to novel plexins. The polypeptides may be produced recombinantly from transformed host cells and from the disclosed plexin encoding nucleic acids or purified from human cells. The invention provides isolated plexin hybridization probes and primers capable of specifically hybridizing with the disclosed plexin genes, plexin-specific binding agents such as specific antibodies, and methods of making and using the subject compositions in diagnosis, therapy and in biopharmaceutical industry. The invention also provides novel plexin neuropilin multimeric receptor complexes for semaphorins and methods of use thereof, including but not limited to, the treatment and diagnosis of neurological disease and neuroregeneration, immune modulation, and viral and oncological diseases.

II ERNATIONAL SEARCH REPORT

Int. ional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N15/62 C12N15/63 C07K14/705 C07K16/28
C12P21/02 A61K38/17 A61K39/395 G01N33/53

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 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, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, SCISEARCH, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EMBL DATABASE EMHUM4:HSAB2313; ACCESSION-NO: AB002313, 1 July 1997 (1997-07-01), XP002157964	1-5
Y	the whole document & DATABASE SWALL:O15031; ACCESSION-NO: O15031, 1 January 1998 (1998-01-01), the whole document & NAGASE, T. ET AL.: "Prediction of the coding sequences of unidentified human genes. VII. The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro" DNA RESEARCH, vol. 4, 1997, pages 141-150, XP002102085 page 142 -page 150 'Results and Discussion' figure 3; tables 1,2	6-9

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

[X] 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

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"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
6 August 2001	31.08.01

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EMBL DATABASE EM_HUM:AB014520; ACCESSION-NO.:AB014520, 15 July 1998 (1998-07-15), XP002173834	1-5
Y	the whole document & ISHIKAWA, K.-I. ET AL.: "Prediction of the coding sequences of unidentified human genes. X. The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro" DNA RESEARCH, vol. 5, 30 June 1998 (1998-06-30), pages 169-176, XP002121149 page 172 -page 176 * 'Results and Discussion' * figures 1,2; tables 1-3	6-9

X	EMBL DATABASE EMHUM4:HS5211110; ACCESSION-NO: U52111, 9 May 1996 (1996-05-09), XP002173835	1-5
Y	page 12 -page 13 * Gene="PLXB3" and product="plexin-related protein" *	6-9

X	EMBL DATABASE EMHUM6:HSOCTPROT; ACCESSION-NO: X87831, 6 February 1996 (1996-02-06), XP002173836 the whole document	1-3

X	EMBL DATABASE EM_OV:XLPLEX; ACCESSION-NO:D38175, 25 August 1995 (1995-08-25), XP002173837 the whole document & OHTA, K. ET AL.: "Plexin: a novel neuronal cell surface molecule taht mediates cell adhesion via a homophilic binding mechanism in the presence of calcium ions" NEURON, vol. 14, 1995, pages 1189-1199, XP001013227	1-3

X	WO 99 04263 A (THE JOHN HOPKINS UNIVERSITY SCHOOL OF MEDICINE) 28 January 1999 (1999-01-28)	10,11
Y	page 5, line 9 -page 10, line 16 page 16, line 6 -page 22, line 3 page 23, line 22 -page 24, line 18 page 29, line 6 -page 32, line 4	12,13

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	KAMEYAMA, T. ET AL.: "Identification of a cell surface protein plexin (the B2) in mouse, and its expression in developing nervous systems" NEUROSCIENCE RESEARCH SUPPLEMENT, vol. 18, 1993, page S115 XP000945106 the whole document	6-9
Y	COMEAU, M. ET AL.: "A poxvirus-encoded semaphorin induces cytokine production from monocytes and binds to a novel cellular semaphorin receptor, VESPR" IMMUNITY, vol. 8, April 1998 (1998-04), pages 473-482, XP000945259 cited in the application page 478 -page 480 'Discussion'	12,13
A	MAESTRINI, E. ET AL.: "A family of transmembrane proteins with homology to the MET-hepatocyte growth factor receptor" PROC.NATL.ACAD.SCI.USA, vol. 93, no. 2, 1996, pages 674-678, XP000941746 the whole document	1-9
P,X	TAMAGNONE, L. ET AL.: "Plexins are a large family of receptors for transmembrane, secreted, and GPI-anchored semaphorins in vetebrates" CELL, vol. 99, 1 October 1999 (1999-10-01), pages 71-80, XP000941702	1-5
P,Y	page 72 -page 78 'Results' and 'Discussion'	6-9,12, 13
P,Y	TAKAHASHI, T. ET AL.: "Plexin-Neuropilin-1 complexes form functional semaphorin-3A receptors" CELL, vol. 99, 1 October 1999 (1999-10-01), pages 59-69, XP000941701 page 60 -page 67 'Results' and 'Discussion'	12,13
A	NAKAMURA, F. ET AL.: "Neuropilin-1 extracellular domains mediate semaphorin D/III-induced growth cone collapse" NEURON, vol. 21, November 1998 (1998-11), pages 1093-1100, XP002174004 cited in the application the whole document	10-13

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/23365

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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 10,11 (partially)
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 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:

see additional sheet

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 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.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 10-13 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.
Although claim 14 is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 10,11 (partially)

Claims 10 and 11 concern a methods which comprise the administration of an agent capable of interfering with the association between a plexin and a neuropilin. Since in the specification this agent is exemplified only to be an antibody raised against the plexin and since it is completely unclear which kind of substances besides said antibody also will be capable of interfering with the association between a plexin and a neuropilin, the scope of said claims is totally ambiguous and undefined as far as any kind of substance other than an antibody raised against the plexin is concerned.
Therefore, the search in respect of claims 10 nad 11 has been limited to methods comprising the administration of an antibody raised against the plexin and which is capable of interfering with the assiciation between a plexin and a neuropilin.

The applicant's attention is drawn to the fact that claims, or parts of 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. Claims: 1-9,12-14 (partially)

Claims 1-9,12-14 (partially) refer to the isolation and cloning of a member of the plexin family, plexin B-2. Antibodies specifically binding to this polypeptide, a fusion protein, and methods of diagnosing for tumors, treating a disorder involving aberrant immune regulation involving a signal pathway between plexin and a neuropilin, and suppressing aberrant cell growth, all methods by using either the polypeptide or the antibodies directed against the plexin B-2.

2. Claims: 1-9,12-14 (partially)

Claims 1-9,12-14 (partially) refer to the isolation and cloning of a member of the plexin family, plexin B-3. Antibodies specifically binding to this polypeptide, a fusion protein, and methods of diagnosing for tumors, treating a disorder involving aberrant immune regulation involving a signal pathway between plexin and a neuropilin, and suppressing aberrant cell growth, all methods by using either the polypeptide or the antibodies directed against the plexin B-3.

3. Claims: 1-9,12-14 (partially)

Claims 1-9,12-14 (partially) refer to the isolation and cloning of a member of the plexin family, plexin D-1. Antibodies specifically binding to this polypeptide, a fusion protein, and methods of diagnosing for tumors, treating a disorder involving aberrant immune regulation involving a signal pathway between plexin and a neuropilin, and suppressing aberrant cell growth, all methods by using either the polypeptide or the antibodies directed against the plexin D-1.

4. Claims: 1-9,12-14 (partially)

Claims 1-9,12-14 (partially) refer to the isolation and cloning of a member of the plexin family, plexin A-4. Antibodies specifically binding to this polypeptide, a fusion protein, and methods of diagnosing for tumors, treating a disorder involving aberrant immune regulation involving a signal pathway between plexin and a neuropilin, and suppressing aberrant cell growth, all methods by using either the polypeptide or the antibodies directed against the plexin A-4.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

5. Claims: 10,11

Claims 10 and 11 refer either to a method of suppressing or altering aberrant cell growth involving a signalling pathway between a plexin and a neuropilin in a mammal or to a method of treating, suppressing or altering a disorder involving aberrant immune regulation involving a signalling pathway between a plexin and a neuropilin in a mammal, both methods comprises the administration of an agent in general being capable of interfering with the association between the plexin and neuropilin to said mammal.

II ERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/US 00/23365

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9904263 A	28-01-1999	AU 8405398 A	10-02-1999