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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: NEURAL REGENERATION PEPTIDE AND METHODS FOR THEIR USE IN TREATMENT OF BRAIN DAMAGE

(57) Abstract: The invention discloses a family of neuronal migration-inducing, proliferation-promoting and neurite outgrowth promoting factors, termed NRP compounds, and provides compositions and methods for the use of NRP compounds in the treatment of brain injury and neurodegenerative disease. NRP-1 compounds induce neurons and neuroblasts to proliferate and migrate into areas of damage caused by acute brain injury or chronic neurodegenerative disease, such as stroke, trauma, nervous system infections, demyelinating diseases, dementias, and metabolic disorders. NRP compounds may be administered directly to a subject or to a subject's cells by a variety of means including orally, intraperitoneally, intravascularly, and directly into the nervous system of a patient.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/26782

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) : A61K 38/00

US CL : 514/12

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)
U.S. : 514/12

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 practicable, search terms used)
USPAT, USPGPUBS, EPO, JPO, DERWENT, all commercial sequence databases

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/38100 A1 (AKERBLOM et al) 16 October 1997 (16.10.1997), entire document, especially pp.38-39.	1-5, 25 and 39
X	US 5,834,192 A (AKERBLOM et al) 10 November 1998 (10.11.1998), entire document, especially columns 27-32.	1-5, 25 and 39
X	US 6,262,024 B1 (CUNNINGHAM et al) 17 July 2001 (17.07.2001), entire document, especially columns 43-50.	1-5, 8-14, 25-29 and 39
X	WO 98/11136 A1 (DIN et al) 19 March 1998 (19.03.1998), entire document, especially pp.35-41.	1-5, 25 and 39
X	CUNNINGHAM et al. Identification of a survival-promoting peptide in medium conditioned by oxidatively stressed cell lines of nervous system origin. J Neurosci. 1998, 15 September 1998, Vol. 18, No. 18, pages 7047-7060, entire document.	1-5, 8-14, 25-29 and 39



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 application or patent 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

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INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim 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. ☐ Claim 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:
Please See Continuation Sheet

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.: 1-5, 8-14, 25-29 and 39

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I-XVI, claim(s) 1-5, 8-14, 25-29, 39 are drawn to a neural regeneration peptide (NRP) compound comprising at least one amino acid sequence comprising at least one [A]PG[R,S] domain, and having at least one biological effect selected from the group consisting of neuronal migration, neural proliferation, neural outgrowth, promoting activities, and neural survival, further comprising at least one additional amino acid domain selected from the group consisting of [A]PG[R,S], PE, [A,G]RR and ARG, and having the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, and SEQ ID NO: 26; and a method for promoting neural regeneration, comprising the step of delivering to a neural tissue, a pharmacological effective amount of an NRP compound, having the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, and SEQ ID NO: 26, or wherein said NRP .

Groups XVII-XXVII, claim(s) 6,7, and 15-24 are drawn to a nucleotide sequence encoding an NRP, wherein said nucleic acid sequence is SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, and SEQ ID NO: 19.

Groups XXVIII-XXXVIII, claim(s) 13 and 14 are drawn to a method for promoting neural regeneration, comprising the step of delivering to a neural tissue, a pharmacological effective amount of an NRP compound, wherein said NRP is encoded by a nucleic acid of claim 6, having the nucleic acid sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, and SEQ ID NO: 19.

Group XXXIX, claim(s) 30-38 is drawn to methods for promoting neuronal proliferation or migration, neurite outgrowth, neuronal survival, and treating a patient having spinal cord injury, comprising administering an effective amount of an NRP compound to said neuron.

Group XL, claim(s) 40-45 is drawn to methods for determining the presence of an NRP, determining the pharmacological efficacy of an NRP, and comparing the efficacy of a test molecule.

The inventions listed as Groups I-XVI do not meet the requirements for Unity of Invention for the following reasons:

Groups I-XXVII are drawn to separate, distinct inventions and are distinguished from each other because the special technical features which define them by chemical and physical characteristics i.e. structure/function, as well as biological functions are different and these special technical features are not shared by each invention as evidenced by the different nucleic acid structures. Since these special technical features are not shared by each product and since the common features do not establish an advance over the prior art, the inventions of Groups I-XXVII do not form a single inventive concept within the meaning of Rule 13.2.

Groups XVIII-XL are drawn to methods different in design and performance, and which do not share the same or a corresponding special technical feature which define the contribution of each invention. The methods of Groups XVIII-XL do not share a corresponding special technical feature because the methods are practiced with materially different process steps for materially different purposes and each method requires different starting materials, process steps and goals. Since these special technical features are not shared by each process, and since the common features do not establish an advance over the prior art, the inventions of Groups XVIII-XL do not form a single inventive concept within the meaning of Rule 13.2.

The inventions of Groups I-XXVII are separate and distinct from the inventions of Groups XVIII-XL because the invention of Groups I-XXVII may be used in other methods than those of Groups XVIII-XL, such as in identification of a ligand to the protein of interest or in making an antibody to said protein.