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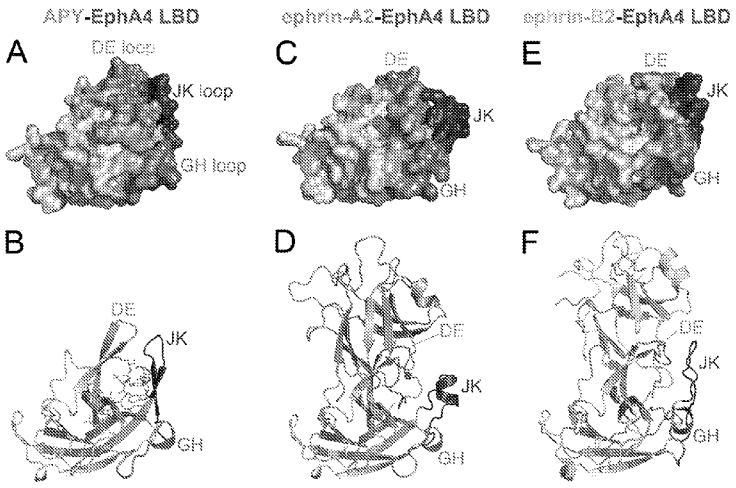
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

[Continued on next page]

(54) Title: EPHA4 CYCLIC PEPTIDE ANTAGONISTS FOR NEUROPROTECTION AND NEURAL REPAIR

FIG. 1



(57) Abstract: The present specification discloses APY cyclic peptides having EphA4 antagonistic activity, pharmaceutical compositions containing such EphA4 antagonists, and methods and uses of treating an EphA4-based disease, disorder or pathology in an individual using such APY cyclic peptides or pharmaceutical compositions.

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
10 March 2016

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/40649

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/00; G01N 33/68 (2015.01)
CPC - A61K 38/00; G01N 33/6863
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(8): A61K 38/00, 47/48, 49/00; C07K 14/52; G01N 33/68 (2015.01)
CPC: A61K 38/00, 47/48246, 49/0002; C07K 14/52; G01N 33/6863

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)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Dialog ProQuest; IP.com; Google; Google Scholar; 'EphA4,' receptor, antagonist, cyclic, peptide, 'amino acids'

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0180823 A1 (PASQUALE, E et al.) September 16, 2004; figures 15A, 19; SEQ ID NO: 20; paragraphs [0014], [0040], [0058]-[0061], [0131]; Table 1	1-3
Y	CARNEGIE, Structure And Properties Of A Homologue Of Glutathione. Biochem. J. 1963, Vol. 89; pages 471-478; page 471, column 1, paragraph 1 to column 2, paragraph 2; page 478, column 1, paragraph 3.	1-3
A	US 2008/0254023 A1 (BARTLETT, PF et al.) October 16, 2008; abstract	1-3

☐ 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 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
18 November 2015 (18.11.2015)	29 DEC 2015
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/40649

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/40649

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

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.: 4-39
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:

-***-Please See Supplemental Page-***-

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 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.:

1 (in-part), 2 and 3 + A-P-Y-C-V-Y-R-BetaA-S-W-S-C

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/US15/40649

-***-Continued from Box No. III: 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+, Claims 1-3 and the sequence: A-P-Y-C-V-Y-R-BetaA-S-W-S-C are directed toward an EphA4 receptor antagonist comprising a cyclic peptide having a length of 12 amino acids.

The EphA4 receptor antagonist will be searched to the extent that the peptide encompasses the sequence A-P-Y-C-V-Y-R-BetaA-S-W-S-C (first amino acid sequence of an exemplary antagonist peptide). Applicant is invited to elect additional fully specified antagonist peptide sequence(s)(i.e. with no optional species or residues) to be searched. Additional antagonist peptide sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1(in-part), 2 and 3 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass this antagonist peptide sequence. An exemplary election would be an antagonist peptide encompassing the sequence BetaA-P-Y-C-V-Y-R-Beta-A-S-W-S-C. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

Groups I+ share the technical features including: an EphA4 receptor antagonist comprising a cyclic peptide having a length of 12 amino acids and including the sequence X1-X2-X3-C4-X5-X6-X7-BA8-X9-W-X11-C12 (SEQ ID NO: 3), wherein X1 is independently BA, D-A, A, E, G, Q, D, L, S, F, or Y; X2 is independently P, A, G, Ahx, Ava, .gamma.Abu, BA or Sar; X3 is independently Y, F, W, V, L, H or I; X5 is independently V or L; X6 is independently Y, F, W or H; X7 is independently any amino acid; X9 is independently any amino acid; and X11 is independently any amino acid; wherein C4 and C12 form a disulfide bridge; and wherein C12 is optionally amidated.

However, these shared technical features are previously disclosed by US 2004/0180823 A1 to Pasquale et al. (hereinafter 'Pasquale') in view of the article 'Structure and Properties of a Homologue of Glutathione' by Carnegie (hereinafter 'Carnegie').

Pasquale discloses an EphA4 receptor antagonist (EphA4 receptor antagonist; Figures 15A, 19; SEQ ID NO: 20; paragraphs [0014], [0040]), comprising a cyclic peptide (comprising a cyclic peptide; paragraphs [0058], [0131]) having the sequence APYCVYRGSWSC (having the sequence APYCVYRGSWSC; Figure 19, Table 1) wherein C4 and C12 form a disulfide bridge (wherein an intramolecular disulfide bond exists between thiol groups of the cysteines (wherein C4 and C12 form a disulfide bridge); paragraph [0131]). Pasquale further discloses wherein the peptide may include substitutions at any position of the peptide to produce analogues (systematic substitution of one or amino acids to produce analogues (wherein the peptide may include substitutions at any position of the peptide to produce analogues); paragraphs [0058], [0063]); including the use of synthetic or non-naturally occurring amino acids (including the use of synthetic or non-naturally occurring amino acids; paragraph [0059]), such as modified forms of alanine (including modified forms of alanine; paragraph [0061]).

Pasquale does not disclose wherein the peptide comprises BA8.

Carnegie discloses a homologue of glutathione (a homologue of glutathione; title), wherein the C-terminal glycine has been replaced by B-alanine (wherein the C-terminal glycine has been replaced by B-alanine; page 471, column 1, paragraphs - 2). Carnegie further discloses wherein the pK values of the homologue are higher than the values for the original peptide (wherein the pK values of the homologue are higher than the values for the original peptide; page 478, column 1, paragraph 3).

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Pasquale to have included a substitution found in nature, such as substitution of Beta-alanine for glycine, as disclosed by Carnegie, in the peptide antagonist disclosed by Pasquale, in order to modify the pK of the peptide to produce BA8, and potentially enhance the binding properties of the analogue, based on the disclosure of Carnegie.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Pasquale and Carnegie references, unity of invention is lacking.