Title: COMPOSITIONS AND METHODS FOR MODULATING AT2R ACTIVITY

Abstract: New polypeptide agonists of AT2R are disclosed, as well as pharmaceutical compositions comprising the agonists, methods of their use in the treatment of diseases, conditions or disorders characterized by insufficient AT2R activity or excessive AT1R activity, and methods of their use as laboratory reagents for research purposes.
Published: (88) Date of publication of the international search report: 28 July 2016

— 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))
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07K 9/00, A61K 38/08 (2016.01)
CPC - C07K7/14, C07K7/02, C07K7/00

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): C07K 9/00, A61K 38/08 (2016.01)
CPC: C07K7/14, C07K7/02, C07K7/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC: 514/16.4, 435/375, 514/17.7, 435/375

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, Google Scholar, Google Web, search terms: AT2R protein, AT1R MTER, NHE6, ErbB3, Nitric Oxide Synthase, ErbB3 and hypertension, ALS, Alzheimer's, Parkinson's, muscular dystrophy, spinal cord injury, traumatic brain injury, brain lesions, nephropathy, hypertension, Lys-Pro-Leu-Lys-Pro-Trp, KPLKPW, KPIPKW

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 2013/158628 A1 (NEW YORK UNIVERSITY) 24 October 2013 (24.10.2013) para [0018], [0038], [0052], [0063], [0064], [0065], [0066], SEQ ID NO: 4</td>
<td>1,12,23/1,24,25, (27, 29-30)/(24,25)</td>
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<td>Y</td>
<td>A. et al. Chronic AT2 receptor activation increases renal ACE2 activity, attenuates AT1 receptor function and blood pressure in obese Zucker rats. Kidney International (November 2013) vol 84, no 5, pp 9317939, abstract, pg 934, col 1, para 3, pg 935, col 2, para 2, pg 936, col 2, para 2</td>
<td>2-4, 7-6, 10-1 1, 13, 18-21</td>
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<td>Y</td>
<td>Guimond et al. The Angiotensin II Type 2 Receptor in Brain Functions: An Update. International Journal of Hypertension. (2012), Volume 2012 Article ID 351758, 18 pages, doi:10.1 155/2012/351758, pg 3, col 1, para 1, para 2, pg 6, col 1 para 1, para 6, col 2 para 2, pg 9, col 1, para 1, P.16</td>
<td>5, 14, 22</td>
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<td>Y</td>
<td>US 2012/0157513 A1 (Li et al.) 21 June 2012 (21.06.2012) para [0023], [0029], [0044]</td>
<td>9, 16, 19, 21</td>
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Further documents are listed in the continuation of Box C.

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

"Z" document member of the same patent family

Date of the actual completion of the international search
10 May 2016 (10.05.2016)

Date of mailing of the international search report
03 JUN 2016

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Authorized officer: Lee W. Young
PCT Helpdesk: 371-272-4300
PCT OSP: 371-272-7774

Form PCT/ISA/2 10 (second sheet) (January 2015)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Salomone et al. Intrarenal Dopamine D1-Like Receptor Stimulation Induces Natriuresis via an Angiotensin Type-2 Receptor Mechanism. Hypertension. (January 2007) vol 49, no 1, pp 155-161 abstract, pg 156, col 1, para 3-7, pg 160, col 1, para 4, col 2, para 4 - pg 161, col 1, para 1</td>
<td>17</td>
</tr>
</tbody>
</table>
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/61597

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.:
   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:

---------------See extra 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 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.:

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.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)
Continuation of 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.

Group I: Claims 1-23, directed to methods of activating AT2R or inhibiting AT1R proteins in cells with an AT2R agonist peptides.

Group II: Claims 24-30, directed to a pharmaceutical composition comprising a peptide.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

Group II does not require a method of activating AT2R or inhibiting AT1R in a mammal, as required by Group I.

Group I does not require a pharmaceutical composition, as required by Group II.

Common Technical Features

The common technical feature shared by Groups I and II is a polypeptide comprising an amino acid sequence that corresponds to the formula: AI-A2-A3-A4-A5-A6 wherein AI is Lys, A2 is Pro, 3Hyp or 4Hyp, A3 is Leu or Lle, A4 is Lys, A5 is Pro, 3Hyp or 4Hyp, and A6 is Trp. However, this shared technical feature does not represent a contribution over prior art, in view of WO 2013/1358628 A1 to NEW YORK UNIVERSITY (hereinafter 'NYU'). NYU teaches AT2R agonist Arg-Pro-Leu-Lys-Pro-Trp (SEQ ID NO: 41 (para [0018]). NYU does not expressly teach the claimed peptide Lys-Pro-Leu-Lys-Pro-Trp (SEQ ID NO 2), however, it would have been obvious to experiment with variants of NYU peptide, such as to substitute Arg with Lys, because both are positive charged amino acids that have similar structure, and thus would be likely to have similar activities.

As the technical feature was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I and II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.