Title: CXCR4 UP- AND DOWN-REGULATION FOR TREATMENT OF DISEASES OR DISORDERS

Abstract: The present invention includes a method of treating or preventing HAND in a subject in need thereof, wherein the method comprises administering to the subject a composition that down-regulates ferritin heavy chain (FHC). The present invention further includes a method of treating or preventing HAND in a subject in need thereof, wherein the method comprises administering to the subject a composition that decreases the concentration, expression level and/or activity of IL-1β. The present invention further includes a method of treating or preventing a subject in need thereof a disease or condition associated with CXCR4 up-regulation, such as but not limited to cancer, metastasis, liver fibrosis (including HrV-associated liver fibrosis), or HfV infection, wherein the method comprises administering to the subject a composition that up-regulates FHC.
### A. CLASSIFICATION OF SUBJECT MATTER

**IPC(8)**: A61K 39/21, A61K 39/00, C12Q 1/68, C12P 19/34 (2015.01)

**CPC**: C07K 14/005, A61K 38/00, C12Q 1/6883, C12N 15/10

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)

USPC- 424/208.1

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

IPC(8): A61K 39/21, A61K 39/00, C12Q 1/68, C12P 19/334 (2015.01)

CPC: C07K 14/005, A61K 38/00, C12Q 1/6883, C12N 15/10; USPC: 424/208.1 , 424/184.1, 435/6.1 , 435/91.1

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

PatentBase (PGIB, USPT, USOC, EPAB, JPAB, DWPI, TDBD), FreePatentsOnline (US Pat, Pypub, EPO, IPO, WIPO, NPL),

GoogleScholar (PL, NPL); search terms: HIV associated neurocognitive disorders (HAND), ferritin heavy chain, IL-1 beta, IL-1 receptor antagonist, CXCR4, opioid.

### 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>Y</td>
<td>Pitcher et al., Disruption of neuronal CXCR4 function by opioids: Preliminary evidence of Ferritin Heavy Chain as a potential etiological agent in neuroAIDS, Journal of Neuroimmunology 224, 66-71 (2010) Abstract, pg 1, para 1, pg 3, para 3 to pg 4, para 1</td>
<td>1-8</td>
</tr>
<tr>
<td>Y</td>
<td>WO 2004/045561 A2 (Stevenson et al.) 03 June 2004 (03.06.2004) Abstract, pg 2, ln 12-31 ; pg 4, ln 10-24, pg 12, ln 1-6, pg 42, ln 19-24, pg 33, ln 24-28</td>
<td>1-8</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

**Note:**
- "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: 23 March 2015 (23.03.2015)

Date of mailing of the international search report: 13 APR 2015

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. 571-273-3201

Authorized officer: Lee W. Young

PCT Helpdesk: 571-272-4300
PCT GSP: 571-272-7774

Form PCT/ISA/2 10 (second sheet) (January 2015)
INTERNATIONAL SEARCH REPORT

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:

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 1-8, directed to a method comprising administering to the subject a therapeutically effective amount of an agent that down-regulates FHC in the subject.

Group II. claims 9-17, directed to a method comprising administering to the subject a therapeutically effective amount of an agent that decreases that concentration, expression level and/or activity of IL-1-beta in the subject.

Group III. claims 18-26, directed to a method comprising administering to the subject a therapeutically effective amount of an opioid agonist, whereby the disease or condition associated with CXCR4 up-regulation is treated or prevented.

********** Continued in the supplemental box **********

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. 1-8

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 III:

The of inventions of Groups I-III listed above 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

The special technical feature of Group I is administering an agent that down-regulates FHC in the subject, using an amount therapeutically effective for treating or preventing HAND in the subject, not required in any other groups.

The special technical feature of Group II is administering an agent that decreases the concentration, expression level and/or activity of IL-1-beta in the subject, using an amount therapeutically effective for treating or preventing HAND in the subject, not required in any other groups.

The special technical feature of Group III is a method comprising treating or preventing a disease or condition associated with CXCR4 up-regulation, not required in any other groups.

Common Technical Features

Groups I-III share the technical feature of a method of treating or preventing a disease or condition in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of an agent whereby disease or condition is treated or prevented in the subject. Groups I-III share the technical feature of treating or preventing HIV associated neurocognitive disorder in a subject in need thereof. However, this technical feature is not a unifying technical feature as it does not make a contribution over the prior art in view of anticipatory WO 2006/101920 A2 to Dewhurst et al. (hereinafter Dewhurst). Dewhurst discloses a method of treating or preventing a disease or condition in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of an agent whereby disease or condition is treated or prevented in the subject, wherein the disease or condition is HIV associated neurocognitive disorder (Abstract, pg 1, in 23-25: a method of treating or preventing HIV-I associated dementia comprising administering to the subject a therapeutically effective dose of a modulator . . . ).

Therefore, Groups I-III lack unity under PCT Rule 13.