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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:

9 August 2012

(54) Title: TREATMENT AND PREVENTION OF HEPATOCELLULAR CARCINOMA WITH CHEMOKINE RECEPTOR MODULATORS

(57) Abstract: The present invention is directed to means for specifically elevating the level of the CCR5 and CCR1 ligand RANTES in the blood of subjects afflicted with, or predisposed to developing HCC. Advantageous dosing regimes, formulations, derivatives and conjugates of RANTES enabling prolonged blood retention may be particularly useful for treating, preventing or suppressing the onset and progression of HCC subsets. In addition, the use of CCR5 and/or CCR1 inhibitors is contemplated.



WO 2012/052995 A3

INTERNATIONAL SEARCH REPORT

international application no.

PCT/IL 11/00816

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/00, 31/7088; C12N 15/113 (2012.01)

USPC - 514/19.2, 19.3, 44A

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, 31/7088; C12N 15/113 (2012.01)

USPC - 514/19.2, 19.3, 44A

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)

PubWest (PGPB,USPT,USOC,EPAB,JPAB); PubMed (MEDLINE)

RANTES, CCL5, D17S136E, MGC17164, SCYA5, SISd, TCP228, CCR5, hepatocellular carcinoma, blood, serum, plasma

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 2006/0084628 A1 (POTTAGE) 20 April 2006 (20.04.2006) para [0006], [0015], [0017], [0018]	27-28, 31-33 ----- 22-24, 29-30, 34-36
Y	US 7,217,700 B2 (VICARI et al.) 15 May 2007 (15.05.2007) col 4, ln 7-12; col 7; col 8, ln 1-9;	1-26
Y	Aukrust et al., Circulating levels of RANTES in human immunodeficiency virus type 1 infection: effect of potent antiretroviral therapy. J Infect Dis., April 1998, vol 177, no 4, pp 1091-6; pg 1092, col 1, para 1, 7; pg 1093, Fig 1; pg 1095, Fig 3b	1-26
Y	JOO et al., Expression of beta-catenin in hepatocellular carcinoma in relation to tumor cell proliferation and cyclin D1 expression. J Korean Med Sci., April 2003, vol 18, no 2, pp 211-7; pg 212, col 1, para 3; pg 212, col 2, para 3, 6; pg 216, col 1, para 1; pg 216, col 2, para 3	4-6, 35-36
Y	US 2006/0165650 A1 (PAVONE et al.) 27 July 2006 (27.07.2006) para [0011], [0022], [0226]	20-21, 26, 34
Y	KIM et al., RNAi-mediated CCR5 silencing by LFA-1-targeted nanoparticles prevents HIV infection in BLT mice. Mol Ther., February 2010 (published online 08 December 2009), vol 18, no 2, pp 370-6; pg 371, col 1, para 1; pg 373, Fig 3b	29
Y	GONZALEZ et al., A hammerhead ribozyme targeted to the human chemokine receptor CCR5. Biochem Biophys Res Commun., 20 October 1998, vol 251, no 2, pp 592-6; pg 592, col 2, para 2; pg 594, Fig 4	30

☐ 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

"&" document member of the same patent family

Date of the actual completion of the international search

22 May 2012 (22.05.2012)

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Name and mailing address of the ISA/US

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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 1-26, directed to a method for treating hepatocellular carcinoma (HCC) or for inhibiting or delaying the onset of an HCC tumor, comprising administering to a subject in need thereof an isolated RANTES polypeptide or derivative thereof, so as to enhance the level of RANTES or a derivative thereof specifically in the blood plasma of the subject.

Group II: claims 27-36, directed to a method for ameliorating the onset of hepatocellular carcinoma, comprising administering to a subject in need thereof at least one inhibitor of CCR5.

----- 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 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.

Continuation of Box No. III: Observations where unity of invention is lacking

The inventions listed as Groups I - 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:

The special technical feature of the claims of Groups I and II are indicated in the Group descriptions, above.

The only common technical element shared by the above groups is that they are related to treatment or amelioration of hepatocellular carcinoma. This does not represent an improvement over the prior art of US 2002/0034494 A1 to Vicari et al. (hereinafter "Vicari") teaches a method for treating hepatocellular carcinoma (para [0051]) comprising administering to a subject in need thereof an isolated RANTES polypeptide or derivative thereof (a method of treating disease states comprising administering to an individual in need thereof an amount of chemokine sufficient to increase the migration of immature dendritic cells to the site of antigen delivery... a chemokine such as...RANTES; para [0018]).

Therefore, the inventions of Group I and Group II lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.