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- (71) **Applicant (for all designated States except US):** HEALTH RESEARCH, INC. [US/US]; One University Place, Rensselaer, NY 12144-3447 (US).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** PHILPOTT, Sean [US/US]; 24 Oak St., Defreestville, NY 12144 (US). WEISER, Barbara [US/US]; 345 Millers Corner Road, East Greenbush, NY 12061 (US). BURGER, Harold [US/US]; 345 Millers Corner Road, East Greenbush, NY 12061 (US).
- (74) **Agents:** KOWALSKI, Thomas, J. et al.; Frommer, Lawrence & Haug LLP, 745 Fifth Avenue, New York, NY 10151 (US).
- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
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- Published:**
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- (88) **Date of publication of the international search report:**
2 October 2008

(54) **Title:** HETERODUPLEX TRACKING ASSAY

(57) **Abstract:** A change in viral tropism occurs in many HIV positive individuals over time and may be indicated by a shift in coreceptor use from CCR5 to CXCR4. The shift in coreceptor use to CXCR4 has been shown to correlate with increased disease progression. In patients undergoing HAART, the predominant populations of virus may be shifted back to CCR5- mediated entry soon after the CXCR4-specific strains have emerged. The present invention relates to a diagnostic method to monitor coreceptor use in the treatment and clinical management of human immunodeficiency virus (HIV) infection. The present invention further relates to a diagnostic method applied to HIV-positive individuals undergoing HAART to monitor the suppression of CCR5- or CXCR4-specific strains. The diagnostic methods may be used to assist in selecting antiretroviral therapy and to improve predictions of disease prognosis over time. The methods of the invention include cell-based methods, including cell fusion assays, and molecular-based methods, including heteroduplex tracking assay, to both quantitatively and qualitatively analyze patient-derived HIV for coreceptor usage.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/01243

A. CLASSIFICATION OF SUBJECT MATTER

IPC: C12Q 1/68(2006.01),1/70(2006.01);G01N 33/53(2006.01),33/564(2006.01),33/569(2006.01);A61K 39/42(2006.01)

USPC: 435/5,6,7.2,7.2.7.24,235.1,325,372,372.3

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. : 435/5,6,7.2,7.2.7.24,235.1,325,372,372.3

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)
Please See Continuation Sheet

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 6,727,060 B2 (Philpott et al.) 27 April 2004 (27.04.2004), see abstract, column 1 lines 40-50, column 45 claim 1.	1 ----- 2-22
P, Y	US 2006/0194227 A1 (Philpott et al.) 31 August 2006 (31.08.2006), see abstract, claims 1, 2, 11 and 24.	1-22
Y	JP 2000/325093-A (Brakel et al.) 28 November 2000 (28.11.2000), see para. 25, 27 and 73.	1-12, 14-22
A	NICHOLSON, JANET et al. CCR5 and CXCR4 on memory and naive T cells in HIV infection and response to highly active antiretroviral therapy. JAIDS Journal of Acquired Immune Deficiency Syndrome. 01 June 2001, Vol. 27, No. 2, pages 105-115, see the abstract.	1-22

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	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"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	"&"	document member of the same patent family

Date of the actual completion of the international search

15 January 2008 (15.01.2008)

Date of mailing of the international search report

07 JUL 2008

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

Heather Calamita
Heather Calamita

Telephone No. 571-272-1600

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/01243

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

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

a. type of material

a sequence listing

table(s) related to the sequence listing

b. format of material

on paper

in electronic form

c. time of filing/furnishing

contained in the international application as filed

filed together with the international application in electronic form

furnished subsequently to this Authority for the purposes of search

2. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in 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.

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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:
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 any 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.

BOX 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 1-12 and 14-22, drawn to a method for determining viral load of an AIDS-infected patient, comprising screening molecular clones of AIDS virus to detect CXCR4 receptor usage, wherein said molecular clones are prepared by PCR using the first set of primers in Table 3 of the specification.

Group II:

Claims 1-11 and 13-22, drawn to a method for determining viral load of an AIDS-infected patient, comprising screening molecular clones of AIDS virus to detect CXCR4 receptor usage, wherein said molecular clones are prepared by PCR using the second set of primers in Table 3 of the specification.

The inventions of group I and II are linked by the technical feature OF a method of assessing the degree of HIV progression, determining when to initiate or change the anti retroviral treatment or monitoring the efficacy or the anti retroviral therapy by determining the viral load of a population of acquired immunodeficiency virus using CXCR4 co receptors (X4-specific viral load) in a specimen obtained from an HIV infected patient. This diagnostic method is carried out by heteroduplex tracking assay using RT-PCR technique. However; this technical feature is not considered to be a special technical feature because it does not constitute an addition to the prior art. US 6,727,060 B2 (Philpott et al) is directed to a method of monitoring or diagnosing the efficacy of the anti-retro virus therapy in a patient by quantifying the usage of CXCR4 and/or CCR5 co receptor population of biological clones in a specimen derived from an HIV patient using RT-PCR technique (see Column 13 lines 47-53). Furthermore, groups I and II involve different primer sequences which do not share a significant common structural element and which do not impart a common property or effect.

INTERNATIONAL SEARCH REPORT

International application No.

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Continuation of B. FIELDS SEARCHED Item 3:
PG PUBS, SCIENCE DIRECT,
MEDLINE, EPOLINE, CA PLUS

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US07/01243

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOLY, MARCEL et al. "CXCR4 and CCR5 regulation and expression pattern on T- and monocyte-macrophage cell lineage: Implication for susceptibility to infection by HIV-1." Mathematical Biosciences. 11 May 2005, Vol. 195, pages 92-126, see the whole document especially pages 92, 95 and 117.	1-22
A	WO 99/67429 A1 (UAB RESEARCH FOUNDATION) 29 December 1999 (29.12.1999), See page 4 lines 20-23, page 5 lines 1-4, Claim 12: Examples 3, 4, 7 and 10.	1-22
A	PHILPOTT, S. et al Preferential suppression of CXCR4-specific strains of HIV-1 by anti viral therapy. Journal of Clinical Investigation. February 1999, Vol. 107, No. 4, Pages 431-438, see the whole document.	1-22