Title: COMPOUNDS, KITS AND METHODS FOR CONFERRING CYTOPROTECTION

Abstract: ABCG2, a member of the ATP-Binding Cassette transporters has been identified as a protective pump against endogenous and exogenous toxic agents. ABCG2 was shown to be expressed at high levels in stem cells, and variably regulated during cell differentiation. It is demonstrated herein that functional ABCG2 is expressed in human monocyte-derived dendritic cells by the activation of a nuclear hormone receptor, PPARγ. The present results uncovered a mechanism by which up-regulation of functional ABCG2 expression can be achieved via exogenous or endogenous activation of the lipid activated transcription factor, PPARγ. Thus the invention relates to combined treatments by PPARγ agonists and cytotoxic drugs transportable by ABCG2, various treatments in the field of neoplastic diseases as well as cell therapy, including autologous cell therapy, as well as kits and composition therefore. Method for protecting cells against cytotoxic drugs are also provided.
### INTERNATIONAL SEARCH REPORT

#### A. CLASSIFICATION OF SUBJECT MATTER

**INV. A61K45/06 A61P35/00**

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)

A61K A61P

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

#### 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>
</table>

* 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 document 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.

**S** document member of the same patent family

#### Date of the actual completion of the international search

8 May 2008

#### Date of mailing of the international search report

27 02. 2009

#### Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer

Escolar Blasco, P
INTERNATIONAL SEARCH REPORT

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
      - [X] a sequence listing
      - [ ] table(s) related to the sequence listing

   b. format of material
      - [X] on paper
      - [X] in electronic form

   c. time of filing/furnishing
      - [X] contained in the international application as filed
      - [X] filed together with the international application in electronic form
      - [ ] furnished subsequently to this Authority for the purpose 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:

Form PCT/ISA/210 (continuation of first sheet (1)) (April 2005)
# International Search Report

**International Application No.**
PCT/HU2007/000055

## 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. **X** Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   - Claims 7-11, 21: Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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 additional 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 an additional fee, 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. **X** 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.:

- **see annex**

**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.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6, 13
   Combination of a PPARg agonist and a chemotherapeutic or cytotoxic drug transportable by ABCG2
   ---

2. claims: 7-12
   Cell therapy based on an increase of the expression of PPARg in isolated cells before exposing them to a drug transportable by ABCG2
   ---

3. claims: 14-20
   Nucleotide sequence with ID N° 1, 2, 3, 4, 5 or 6, the vectors comprising them and a repressor protein capable of binding to any of the sequences.
   ---

4. claims: 21-23
   Method and use for alleviating multidrug resistance due to overexpression of ABCG2 by administering a transcription repressor capable of binding to PPARg, a PPARg antagonist, or a siRNA against PPARg.
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<tr>
<td>P,X</td>
<td>MEIER YVONNE ET AL: &quot;ABCG2, encoding the human, breast cancer resistance protein (BCRP), is transactivated by the peroxisome proliferator-activated receptor-gamma (PPARgamma)&quot; HEPATOLOGY, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 44, no. 4, suppl 1, October 2006 (2006-10), page 595A, XP009095303 ISSN: 0270-9139 abstract -----</td>
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<td>X</td>
<td>WO 00/18234 A (UNIV TEXAS [US]) 6 April 2000 (2000-04-06) claims 4,6 -----</td>
<td>1-6</td>
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<td>A</td>
<td>GUTMANN H ET AL: &quot;Distribution of breast cancer resistance protein (BCRP/ABCG2) mRNA expression along the human GI tract&quot; BIOCHEMICAL PHARMACOLOGY, PERGAMON, OXFORD, GB, vol. 70, no. 5, 1 September 2005 (2005-09-01), pages 695-699, XP004996351 ISSN: 0006-2952 -----</td>
<td>1-6</td>
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<tr>
<td>A</td>
<td>HUISMAN MAARTEN T ET AL: &quot;MRP2 (ABCC2) transports taxanes and confers paclitaxel resistance and both processes are stimulated by probenecid&quot; INTERNATIONAL JOURNAL OF CANCER, vol. 116, no. 5, September 2005 (2005-09), pages 824-829, XP002468076 ISSN: 0020-7136 -----</td>
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Form PCT/ISA/210 (continuation of second sheet) (April 2005)