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(71) Applicant (for all designated States except US): BROWN UNIVERSITY [US/US]; 47 George Street, Box 1949, Providence, RI 02912 (US).

(72) Inventors: and

(74) Agent: CHEN, Tan, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210 (US).


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(88) Date of publication of the international search report:
3 November 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SYSTEMS AND METHODS RELATED TO DEGRADATION OF UREMIC TOXINS

(57) Abstract: The present invention generally relates to the treatment of uremic toxins in vivo using uremic toxin-treating enzymes, and/or cells capable of producing uremic toxin-treating enzymes or otherwise reacting with uremic toxins. Non-limiting examples of cases where the treatment of uremic toxins is desired include renal disease or dysfunction, gout, subjects receiving chemotherapy, or the like. In one aspect, the treatment includes an oral delivery composition able to reduce the blood concentration of one or more non-protein nitrogen compounds in vivo. The composition, in some cases, may comprise one, two, or more uremic toxin-treating enzymes, such as urease, uricase or creatininase. In another aspect, the treatment includes an oral delivery composition comprising a cell able to reduce the concentration of one or more uremic toxins in vivo. In some cases, the cell may be designed to overexpress one, two, or more uremic toxin-treating enzymes, such as urease, uricase or creatininase, for example, by transfecting the cell with a correspond-
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K35/74 A61K35/66 A61K38/43 A61P19/06

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 7 A61K

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 practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, PAJ, WPI Data, CHEM ABS Data, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>O'LOUGHLIN J A ET AL: &quot;Microencapsulated enzymes for enteral removal of uremic toxins.&quot; BLOOD PURIFICATION, vol. 21, no. 4-5, 2003, page 359, XP009045592 21ST ANNUAL MEETING OF THE INTERNATIONAL SOCIETY OF BLOOD PURIFICATION (ISBP); UNCASVILLE, CONNECTICUT, USA; SEPTEMBER 08-10, 2003 ISSN: 0253-5068 abstract</td>
<td>1</td>
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A

US 6 126 938 A (GUY ET AL) 3 October 2000 (2000-10-03) claims 1,6-8,15,18,19; example 2

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* 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

* & document member of the same patent family

Date of the actual completion of the International search

23 March 2005

Date of mailing of the International search report

11.08.2005

Name and mailing address of the ISA

European Patent Office, P.B. 5816 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3615

Authorized officer

Ganschow, S
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<td>NISHIDA Y ET AL: &quot;HYPO URICEMIC EFFECT AFTER ORAL ADMINISTRATION IN CHICKENS OF POLY ETHYLENE GLYCOL MODIFIED URICASE ENTRAPPED IN LIPOSOMES&quot; JOURNAL OF PHARMACY AND PHARMACOLOGY, vol. 36, no. 5, 1984, pages 354-355, XP009045559 ISSN: 0022-3573 paragraph ‘DISCUSSION!’</td>
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<td>SPRANDEL U: &quot;Erythrocytes as carrier for therapeutic enzymes—an approach towards enzyme therapy of inborn errors of metabolism.&quot; BIBLIOTHECA HAEMATOLOGICA. 1985, no. 51, 1985, pages 7-14, XP009045546 ISSN: 0067-7957 page 9, paragraph 3 — page 10, paragraph 1</td>
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<td>WO 02/069922 A (L’OREAL; BERNARD, ANNE-LAURE; NICOLAS MORGANTINI, LUC; BIATRY, BRUNO;) 12 September 2002 (2002-09-12) abstract; claims 1,2</td>
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<td>WO 97/26903 A (MCGILL UNIVERSITY; CHANG, THOMAS, M., S; PRAKASH, SATYA) 31 July 1997 (1997-07-31) the whole document</td>
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**INTERNATIONAL SEARCH REPORT**

**Box 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)(e) 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 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 any additional fee.

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

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. **claim: 1**
   
   Orally delivered capsule comprising isolated uricase and/or creatininase and enteric coating

2. **claims: 2-7**
   
   Orally delivered capsule comprising isolated uricase and/or creatininase and a cell transfected with the urease gene, the uricase gene or the creatininase gene

3. **claims: 8-14**
   
   Orally delivered capsule with isolated uricase and/or creatininase comprising an ammonium uptake species

4. **claim: 15**
   
   Oral delivery of uricase or creatininase for the treatment of gout

5. **claim: 16**
   
   Oral delivery of uricase or creatininase to a subject that has been treated with chemotherapy

6. **claims: 17-21**
   
   Oral delivery of uricase or creatininase and administering dialysis to a subject

7. **claims: 22-43**
   
   Oral delivery of cells transfected with or overexpressing a uricase or creatininase gene

8. **claims: 44-53**
   
   Oral delivery of cells transfected with the urease gene, the uricase gene or the creatininase gene wherein at least one cell is not E.coli.

9. **claims: 54-64**
Oral delivery of cells able to reduce a blood concentration of non-protein nitrogen compounds wherein at least one cell is not E.coli.

10. claims: 65-67

Capsules to be delivered orally comprising at least two isolated uremic enzymes.
<table>
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<th>Patent document cited in search report</th>
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