Abstract: Methods are provided for treating Parkinson’s disease, protecting dopaminergic neurons from neurotoxicity and for increasing DJ-1 levels in neurons. Methods are also provided for identifying candidate treatments for Parkinson’s disease.

Fig. 2A
### A. CLASSIFICATION OF SUBJECT MATTER

<table>
<thead>
<tr>
<th>IPC(8)</th>
<th>USPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A61K 38/16; A61P 25/02, 25/16, 25/28 (2013.01)</td>
<td>514/18.2; 3,530/325</td>
</tr>
</tbody>
</table>

According to International Patent Classification (IPC) or to both national classification and IPC

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### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A61K 38/00, 38/16, 38/17; A61P 25/00, 25/02, 25/16, 25/28 (2013.01)

USPC: 514/18.2, 21.4, 6.1, 4, 17.7, 1.1, 1.5, 530/300, 325

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

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### 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>X</td>
<td>US 2005/023326 A1 (HINUMA, S et al.), October 20, 2005, abstract; paragraphs [0026], [0052], [0053], [0076], [0077]</td>
<td></td>
</tr>
</tbody>
</table>

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Further documents are listed in the continuation of Box C.

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* "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; die 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

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Date of the actual completion of the international search

04 April 2013 (04.04.2013)

Date of mailing of the international search report

18 APR 2013

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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: Shane Thomas

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

Form PCT/ISA/210 (second sheet) (July 2009)
### 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 Supplemental Page--".

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.:

   Group 1: Claims 1, 3/1

### 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 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 and 3 are directed toward a method of treating Parkinson's disease or of protecting dopaminergic neurons from neurotoxicity in a subject comprising administering to the subject an amount of humanin or an active humanin analog effective to treat Parkinson's disease or protect dopaminergic neurons.

Group II: Claims 2 and 3 are directed toward a method of increasing DJ-1 expression in a neuron of a subject or of activating STAT-3 in a neuron of a subject comprising administering to the subject an amount of humanin or an active humanin analog effective to increase DJ-1 expression in a neuron or activate STAT-3 in a neuron.

Group III: Claim 16 and 17 are directed toward a humanin analog for treating Parkinson's disease, for treating a subject exhibiting a plurality of pro-dromal symptoms associated with Parkinson's disease, or for protecting dopaminergic neurons from neurotoxicity in a subject.

Group IV: Claim 18 is directed toward a method of identifying a candidate treatment for Parkinson's disease, the method comprising: a) modeling in silico the 3-dimensional form of the humanin analog comprising SEQ IN NO:2, b) testing in silico if a compound from a library of small molecule compounds mimics the modeled 3-dimensional form, and c) determining in vitro if the small molecule identified in b) is chemically stable, thereby identifying the candidate treatment.

The inventions listed as Groups I-IV 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 features of Group I include a method of treating Parkinson's disease or of protecting dopaminergic neurons from neurotoxicity in a subject comprising administering to the subject an amount of humanin or an active humanin analog effective to treat Parkinson's disease or protect dopaminergic neurons, which is not present in Group II. Group II having special technical features including a method of increasing DJ-1 expression in a neuron of a subject or of activating STAT-3 in a neuron of a subject comprising administering to the subject an amount of humanin or an active humanin analog effective to increase DJ-1 expression in a neuron or activate STAT-3 in a neuron, which is not present in Group III. Group III having special technical features including a humanin analog for treating Parkinson's disease, for treating a subject exhibiting a plurality of pro-dromal symptoms associated with Parkinson's disease, or for protecting dopaminergic neurons from neurotoxicity in a subject, which is not present in Group IV. Group IV having special technical features including a method of identifying a candidate treatment for Parkinson's disease, the method comprising: a) modeling in silico the 3-dimensional form of the humanin analog comprising SEQ IN NO:2, b) testing in silico if a compound from a library of small molecule compounds mimics the modeled 3-dimensional form, and c) determining in vitro if the small molecule identified in b) is chemically stable, thereby identifying the candidate treatment.

Groups I-IV share the technical features including a method of treating Parkinson's disease in a subject comprising administering to the subject an amount of humanin or an active humanin analog effective to treat Parkinson's disease.

However, these shared technical features are previously disclosed by US 2005/0233326 A1 to Hinuma, et at. (hereinafter 'Hinuma').

Hinuma discloses a method of treating Parkinson's disease in a subject (Claims 38, 46) comprising administering to the subject an amount of humanin or an active humanin analog effective to treat Parkinson's disease (Claims 38, 46).