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Declaration under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

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(54) Title: METHODS FOR THE TREATMENT OF A TRAUMATIC CENTRAL NERVOUS SYSTEM INJURY

(57) Abstract: Methods of treating a subject with a traumatic central nervous system injury, more particularly, a traumatic brain injury, are provided. The methods comprise a therapy comprising a constant or a two-level dosing regime of progesterone. In one method, a subject in need thereof is administered at least one cycle of therapy, wherein the cycle of therapy comprises administering a therapeutically effective two-level intravenous dosing regime of progesterone. The two-level dosing regime comprises a first time period, wherein a higher hourly dose of progesterone is administered to the subject, followed by a second time period, wherein a lower hourly dose of progesterone is administered to the subject.



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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/079655

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K31/57 A61P25/00

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CUTLER SARAH M ET AL: "Tapered progesterone withdrawal promotes long-term recovery following brain trauma." EXPERIMENTAL NEUROLOGY AUG 2006, vol. 200, no. 2, August 2006 (2006-08), pages 378-385, XP002472537 ISSN: 0014-4886 the whole document</p> <p style="text-align: center;">----- -/--</p>	1-34

☒ 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 *

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

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/079655

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CUTLER ET AL: "Tapered progesterone withdrawal enhances behavioral and molecular recovery after traumatic brain injury"</p> <p>EXPERIMENTAL NEUROLOGY, ACADEMIC PRESS, NEW YORK, NY, US, vol. 195, no. 2, October 2005 (2005-10), pages 423-429, XP005072461</p> <p>ISSN: 0014-4886</p> <p>the whole document</p>	1-34
X	<p>-----</p> <p>DATABASE MEDLINE [Online]</p> <p>US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; July 2006 (2006-07), CUTLER SARAH M ET AL: "Slow-release and injected progesterone treatments enhance acute recovery after traumatic brain injury."</p> <p>XP002472540</p> <p>Database accession no. NLM16870241</p> <p>abstract</p> <p>& PHARMACOLOGY, BIOCHEMISTRY, AND BEHAVIOR JUL 2006, vol. 84, no. 3, July 2006 (2006-07), pages 420-428,</p> <p>ISSN: 0091-3057</p>	1-34
X	<p>-----</p> <p>GOSS C W ET AL: "Behavioral effects and anatomic correlates after brain injury: A progesterone dose-response study"</p> <p>PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR, ELSEVIER, US, vol. 76, no. 2, 2003, pages 231-242, XP002362320</p> <p>ISSN: 0091-3057</p> <p>the whole document</p>	1-34
X	<p>-----</p> <p>HE J ET AL: "Progesterone and allopregnanolone reduce inflammatory cytokines after traumatic brain injury"</p> <p>EXPERIMENTAL NEUROLOGY, ACADEMIC PRESS, NEW YORK, NY, US, vol. 189, no. 2, October 2004 (2004-10), pages 404-412, XP004630619</p> <p>ISSN: 0014-4886</p> <p>the whole document</p> <p>-----</p> <p style="text-align: center;">-/--</p>	1-34

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/079655

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	O'CONNOR ET AL: "Both estrogen and progesterone attenuate edema formation following diffuse traumatic brain injury in rats" BRAIN RESEARCH, ELSEVIER, AMSTERDAM, NL, vol. 1062, no. 1-2, 16 November 2005 (2005-11-16), pages 171-174, XP005161500 ISSN: 0006-8993 the whole document	1-34
X	GUO ET AL: "Progesterone administration modulates AQP4 expression and edema after traumatic brain injury in male rats" EXPERIMENTAL NEUROLOGY, ACADEMIC PRESS, NEW YORK, NY, US, vol. 198, no. 2, April 2006 (2006-04), pages 469-478, XP005358989 ISSN: 0014-4886 the whole document	1-34
X	SHEAR DEBORAH A ET AL: "Progesterone protects against necrotic damage and behavioral abnormalities caused by traumatic brain injury." EXPERIMENTAL NEUROLOGY NOV 2002, vol. 178, no. 1, November 2002 (2002-11), pages 59-67, XP008089484 ISSN: 0014-4886 the whole document	1-20
P, X	WO 2006/102596 A (UNIV EMORY [US]; HOFFMAN STUART W [US]; KELLERMANN ARTHUR L [US]; STEI) 28 September 2006 (2006-09-28) the whole document	1-34
X	WO 02/30409 A (UNIV EMORY [US]; STEIN DONALD GERALD [US]; HOFFMAN STUART WAYNE [US]) 18 April 2002 (2002-04-18) the whole document	1-34
X	JONES NIGEL C ET AL: "The neuroprotective effect of progesterone after traumatic brain injury in male mice is independent of both the inflammatory response and growth factor expression." THE EUROPEAN JOURNAL OF NEUROSCIENCE MAR 2005, vol. 21, no. 6, March 2005 (2005-03), pages 1547-1554, XP002472539 ISSN: 0953-816X the whole document	1-34

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:
Although claims 1-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/079655

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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