**PATENT COOPERATION TREATY**

**PCT**

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

<table>
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<tr>
<th>Applicant’s or agent’s file reference</th>
<th>FOR FURTHER ACTION</th>
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<th>International application No.</th>
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International Patent Classification (8th edition unless older edition indicated)

See relevant information in Form PCT/ISA/237

**Applicant**

THOMAS JEFFERSON UNIVERSITY

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1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

   - **X** Box No. I  Basis of the report
   - Box No. II  Priority
   - Box No. III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - Box No. IV  Lack of unity of invention
   - **X** Box No. V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - Box No. VI  Certain documents cited
   - Box No. VII  Certain defects in the international application
   - Box No. VIII  Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

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**Date of issuance of this report**

17 November 2009 (17.11.2009)

**Authorized officer**

Simin Baharlou

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Form PCT/IB/373 (January 2004)
PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: David S. Resnick
Nixon Peabody LLP
100 Summer Street
Boston, MA 02110-2131

Date of mailing
(day/month/year) 13 NOV 2007

FOR FURTHER ACTION
See paragraph 2 below

Applicant's or agent's file reference
003252059731

International filing date (day/month/year) 11 May 2007 (11.05.2007)
Priority date (day/month/year)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12N 9/20 (2007.01)
USPC - 435/198

Applicant Thomas Jefferson University

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1. This opinion contains indications relating to the following items:
   - [ ] Box No. I  Basis of the opinion
   - [ ] Box No. II  Priority
   - [ ] Box No. III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - [ ] Box No. IV  Lack of unity of invention
   - [x] Box No. V  Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - [ ] Box No. VI  Certain documents cited
   - [ ] Box No. VII  Certain defects in the international application
   - [ ] Box No. VIII  Certain observations on the international application

2. FURTHER ACTION
   If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.
   If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
   For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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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

Date of completion of this opinion
18 September 2007 (18.09.2007)

Authorized officer:
Lee W. Young

Form PCT/ISA/237 (cover sheet) (April 2007)
1. With regard to the language, this opinion has been established on the basis of:
   ☒ the international application in the language in which it was filed.
   ☐ a translation of the international application into ____________ which is the language of a
   translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified
   to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been
   established 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

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) 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.

5. Additional comments:
1. Statement

Novelty (N) Claims 1-33 YES
Claims None NO

Inventive step (IS) Claims None YES
Claims 1-33 NO

Industrial applicability (IA) Claims 1-33 YES
Claims None NO

2. Citations and explanations:

As to claim 1, Hickey teaches a method of treating and/or preventing a neurodegenerative disorder or disease in a subject, the method comprising administering to the subject a pharmaceutical composition comprising an agent that inhibits the activity and/or expression of the Lp-PLA2 protein (col 5, In 16-33). Hickey does not specifically teach identifying a subject with, or at risk of developing a neurodegenerative disease or disorder, however this limitation would have been obvious to one of ordinary skill in the art as it is inherently necessary to identify one in need of treatment for a particular disease in order to treat or prevent that particular disease.

As to claims 2-3, the method of claim 1 is anticipated as described above. Hickey further teaches the method wherein the neurodegenerative disease or disorder is Alzheimer's disease (col 5, In 16-33), and wherein the subject is human, respectively (col 5, In 16-33—Alzheimer's disease is assumed to be a disease of humans).

As to claim 14-15, Hickey teaches an agent which inhibits the expression and/or activity of Lp-PLA2 protein wherein inhibition of the Lp-PLA2 protein reduced a symptom of Alzheimer's Disease (col 5, In 16-33) but does not specifically teach a method of treating and/or preventing Alzheimer's Disease in a subject in need thereof, comprising screening the subject for likelihood of having or developing Alzheimer's Disease, administering to the subject a pharmaceutical composition comprising wherein the subject is identified to have an increased risk or likelihood of developing Alzheimer's Disease determined by step (i) and wherein clinical directs the subject to be treated with an agent which inhibits the expression and/or activity of Lp-PLA2 protein if the subject is at risk of developing Alzheimer's Disease. However, these limitations would have been obvious to one of ordinary skill in the art as they are necessary steps in order to treat or prevent a particular disease.

As to claims 27 and 31-32, the methods of claims 1 and 14 are obvious as described above. Hickey does not specifically teach the method wherein the subject is mammalian and human, respectively, however, Hinkley does teach the treatment of several disease of human origin (col 5, In 16-33). Therefore it would have been obvious to one of ordinary skill in the art to practice the claims as described since the subjects could reasonably be assumed to be mammalian and human.

As to claim 33, Hickey teaches use of an agent which inhibits the expression and/or activity of Lp-PLA2 protein for the preparation of a medicant for treatment and/or prevention of a neurodegenerative disease or disorder (col 5, In 16-33).

Claims 4-5, 23 and 28 lack inventive step under PCT Article 33(3) as being obvious over Hickey in view of the article entitled "Lipoprotein-Associated Phospholipase A2 Is Associated with Risk of Dementia" by Oljen et al. (hereinafter 'Oljen').

As to claims 4, Hickey teaches a method of treating and/or preventing a subject with or at risk of Alzheimer's disease comprising: administering to a subject in need of a pharmaceutical composition comprising an agent which inhibits the activity and/or expression of Lp-PLA2 protein wherein inhibition of the Lp-PLA2 protein reduces or stops a symptom of Alzheimer's disease (col 5, In 16-33). Oljen teaches a method of identifying a subject with, or at risk of developing vascular dementia (and Alzheimer's disease) by association with Lp-PLA2 (p 142). It would have been obvious to one having ordinary skill in the art to combine the treatment method of Hickey with the identification of vascular dementia of Oljen to achieve a treatment method better directed to vascular dementia because Oljen teaches toward treatments for vascular dementia and Alzheimer's disease involving Lp-PLA2.

As to claim 5, the method of claim 4 is obvious as described above. Oljen further teaches the method wherein the vascular dementia is associated with Alzheimer's disease (p 142).

As to claim 23, the method of claim 1 is anticipated as described above. Oljen further teaches assessing cognitive function of said subject (p 141). It would have been obvious to one having ordinary skill in the art to employ the method of claim 1 further comprising assessing cognitive function of said subject after administration of the pharmaceutical composition comprising agents that inhibit Lp-PLA2.

***************Continued in Supplemental Box***************
In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box V. Citations and Explanations

As to claim 28, the method of claim 4 is obvious as described above. Hickey further teaches the method wherein the subject is human (col 5, In 16-33).

Claims 8-9, 10-13, 24-26 and 29-30 lack inventive step under PCT Article 33(3) as being obvious over Hickey in view of the article entitled "Blocking the apolipoprotein E/amyloid-B interaction as a potential therapeutic approach for Alzheimer's disease" by Sadowski et al. (hereinafter "Sadowski").

As to claim 6, Hickey teaches a method of treating and/or preventing a disease or disorder, including Alzheimer’s disease, comprising: administering to the subject in need of a pharmaceutical composition comprising an agent which inhibits the expression and/or activity of the Lp-PLA2 protein (col 5, In 16-33). Sadowski teaches a method for identifying a subject with, or at risk of an abnormal blood brain barrier, and teaches an association between abnormal blood brain barrier and Alzheimer's disease (p 18787). It would have been obvious to one having ordinary skill in the art to combine the treatment of Hickey with the identification of blood brain barrier of Sadowski to achieve a method for treating abnormal blood barrier because Sadowski teaches an association of blood brain barrier abnormality with Alzheimer’s.

As to claims 7-8, the method of claim 6 is obvious as described above. Sadowski teaches the method wherein the abnormal BBB is a permeable blood brain barrier, and wherein the disease or disorder is a neurodegenerative disease or disorder (p 18787), respectively.

As to claim 10, the method of claim 8 is anticipated as described above. Hickey further teaches the method wherein the neurodegenerative disease or disorder is Alzheimer's disease (col 5, In 16-33).

As to claim 11, the method of claim 8 is obvious as described above. Sadowski teaches the method wherein the neurodegenerative disease or disorder is Alzheimer’s disease (p 18787).

As to claim 12, Sadowski teaches a method of identifying a subject with, or at risk of beta amyloid accumulation in the brain and associated symptoms of beta amyloid accumulation with Alzheimer’s disease (p 18787). Hickey teaches a method for treating Alzheimer’s disease comprising: administering to the subject in need of a pharmaceutical composition comprising an agent which inhibits the expression and/or activity of Lp-PLA2 protein (col 5, In 16-33); wherein inhibition of the Lp-PLA2 protein reduces or stops a symptom of Alzheimer’s disease (col 5, In 16-33). It would have been obvious to one having ordinary skill in the art to combine the treatment method of Hickey with the beta amyloid association of Sadowski to achieve a treatment method wherein inhibition of the Lp-PLA2 protein reduces or stops a symptom of beta amyloid accumulation in the brain.

As to claim 13, the method of claim 12 is obvious as described above. Sadowski further teaches the beta amyloid being Abeta-42 (p 18789).

As to claim 24, the method of claim 1 is anticipated as described above. Sadowski further teaches assessment of cerebral blood flow or blood-brain barrier function (p 18787). It would have been obvious to one having ordinary skill in the art to employ the method of claim 1 further comprising monitoring treatment by assessing cerebral blood flow or blood-brain barrier function.

As to claims 25-26, the method of claim 1 is anticipated as described above. Sadowski further teaches a method comprising administering to the subject additional therapeutic agents, including Abeta-lowering therapies, respectively (p 18789).

As to claims 29-30, the methods of claim 6 and 12 are anticipated and obvious, respectively, as described above. Hickey further teaches the method wherein the subject is human (col 5, In 16-33).

Claims 16-18 lack inventive step under PCT Article 33(3) as being obvious over Hickey in view of US 2006/0241130 A1 to Keinan et al. (hereinafter "Keinan").

As to claims 16-18, the method of claim 1 is anticipated as described above. Keinan further teaches a method for treating a medical condition wherein the agent is a nucleic acid, RNA, R spike agent, and an siRNA, respectively (para. [0039], [0281], [0355]). It would have been obvious to one having ordinary skill in the art to combine the treatment of Hickey with the agent of Keinan to achieve a method for treating a neurodegenerative disease having improved delivery.

Claim 9 lacks inventive step under PCT Article 33(3) as being obvious over Hickey in view of Sadowski and in further view of Oijen.

As to claim 9, the method of claim 6 is obvious as described above. Oijen further teaches a method for identifying a subject with vascular dementia (p 142). It would have been obvious to one having ordinary skill in the art to combine the treatment method of Hickey with the identification of blood brain barrier of Sadowski and the identification of vascular dementia of Oijen to achieve a treatment method better directed toward the treatment of an Alzheimer’s involving Lp-PLA2 and because both Hickey and Sadowski are directed to Alzheimer’s.

**********Continued in Supplemental Box**********
In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box V: Citations and Explanations

Claims 19-22 lack inventive step under PCT Article 33(3) as being obvious over Hickey in view of Keinan and in further view of US 2005/0033052 A1 to Leach et al. (hereinafter 'Leach').

As to claims 19-22, the method of claim 16 is obvious as described above. Leach teaches various Lp-PLA2 small molecule inhibitors. wherein the small molecule is 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)(benzyl)aminocarboxy)methyl)-1-(4-
fluorobenzylthio)-5,6-trimethylpyrimidin-4-one, N-(2-diethylaminoethyl)-2-[2-[2-(2,3-difluorophenyl)ethyl]-3-oxo-4,5,6,7-tetrahydro-
cyclopentapyrimidin-1-yl]-1V-(4'-trifluoromethyl-biphenyl-4-imethyl)acetamide, N-(1-(2-methoxyethyl)piperidin-4-yl)-2-[2-(2,3-di-
fluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphenyl-4-il)methyl)acetamide, and methyl 2-[4-(1-(2-fluoro-
dimethoxyethyl)ethyl)-4-oxo-7-(2,3-dimethyl-pyrimidin-4H-y1)acetyl1]yl][1-(trifluoromethyl)-4-biphenylylmethyl)amino]-1-piperidinyl]2-
methylpropanoate, respectively, (para [0001];[0039]).

Claims 1-33 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.