Title: METHODS FOR ATTENUATING PARASITE VIRULENCE

Abstract: Pharmaceutical compositions and methods for the treatment of malaria are presented. Such compositions and methods may target energy-sensing pathways of the malaria parasite, Plasmodium, of parasite host cell, or both. The compositions, in certain aspects of the present invention, target a signalling pathway involving the host AMP-protein activated kinase (AMPK) and/or the parasite AMPK homologue, KIN, which controls parasite replication and virulence.

Fig. 5
Published:
— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(88) Date of publication of the international search report: 1 June 2017

— with sequence listing part of description (Rule 5.2(a))
A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/155 A61P33/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>wo 2011/121109 AI (INST NAT SANTE RECH MED [FR]; BAGHDYOYAN SANDRINE [FR]; PESCHANSKI MARC) 6 October 2011 (2011-10-06) claim 3</td>
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Date of the actual completion of the international search

21 February 2017

Date of mailing of the international search report

03/05/2017

Name and mailing address of the ISA

Economou, Dimitrios

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

Form PCT/ISA/210 (second sheet) (April 2005)
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### INTERNATIONAL SEARCH REPORT

**Box No. I**  
**Nucleotide and/or amino acid sequence(s)**  
(Continuation of item 1.c of the first sheet)

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<td>In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.</td>
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<td>□ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:</td>
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<td>2.</td>
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<td>3.</td>
<td>□ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).</td>
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<td>see additional sheet</td>
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| 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 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.: 1-10, 18-21 (all partially) |

**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.

Form PCT/ISA/21 0 (continuation of first sheet (2)) (April 2005)
This International Searching Authority found multiple (groups of) inventions in this International application, as follows:

1. claims: 1-10, 18-21 (partially)

Methods for attenuating proliferative on of a Plasmodium organi sm or for attenuating proliferative on of a Plasmodium organi sm in a host cell or in an individual, or for treating a Plasmodium infecti on in an individual comprising contacting the organi sm, or the host cell or the individual with an effecti ve amount of a 5' AMP-acti vated protei n ki nase (AMPK) acti vati ng agent, wherei n the acti vati ng agent i s a guani de e.g. buformi n, phenformi n, or metformi n which i s admini stered i n a pharmaceuti cal composition comprisi ng adjuvants, carri ers and di luent and wherei n the composition i s to be admini stered orally or parenteral ly.

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2. claims: 11-13 (completely) ; 1-10, 18-21 (partially)

Methods for attenuating proliferati on of a Plasmodium organi sm or for attenuating proliferative on of a Plasmodium organi sm in a host cell or in an individual, or for treating a Plasmodium infecti on in an individual comprising contacting the organi sm, or the host cell or the individual with an effective amount of a 5' AMP-acti vated protei n ki nase (AMPK) acti vati ng agent, wherei n the acti vati ng agent i s a biguanide e.g. buformi n, phenformi n, or metformi n which i s admini stered i n a pharmaceuti cal composition comprisi ng adjuvants, carri ers and di luent and wherei n the composition i s to be admini stered orally or parenteral ly.

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3. claims: Incompletely) ; 1-10, 18-21 (partially)

Methods for attenuating proliferative on of a Plasmodium organi sm or for attenuating proliferative on of a Plasmodium organi sm in a host cell or in an individual, or for treating a Plasmodium infecti on in an individual comprising contacting the organi sm, or the host cell or the individual with an effective amount of a 5' AMP-acti vated protei n ki nase (AMPK) acti vati ng agent, wherei n the acti vati ng agent i s a salicylate which i s admini stered i n a pharmaceuti cal composition comprisi ng adjuvants, carri ers and di luent and wherei n the composition i s to be admini stered orally or parenteral ly.

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4. claims: 17 (completely) ; 1-10, 15, 16 (partially)

Methods for attenuating proliferative on of a Plasmodium organi sm or for attenuating proliferative on of a Plasmodium organi sm in a host cell or in an individual, or for treating a Plasmodium infecti on in an individual comprising contacting the organi sm, or the host cell or the individual with an
effect ive amount of a 5' AMP-acti vated protei n kinase (AMPK)
acti vati ng agent, wherei n the acti vati ng agent is
resveratrol , nectandri whi ch is admi ni stered i n a
pharmaceuti cal composition compri si ng adjuvants , carri ers
and di luents and wherei n the composition i s to be
admi ni stered oral ly or parenteral ly.

5. c laims: 1-10, 15, 16, 18-21 (al 1 parti al ly)

Methods for attenuati ng prol iferati on of a Pl asmodi um
organi sm or for attenuati ng prol iferati on of a Pl asmodi um
organi sm i n a host cel l or i n an i ndi vi dual , or for treati ng
a Pl asmodi um i nfecti on i n an i ndi vi dual compri si ng contacti ng
the organi sm, or the host cel l or the i ndi vi dual with an
effecti ve amount of a 5' AMP-acti vated protei n kinase (AMPK)
acti vati ng agent, wherei n the acti vati ng agent i s nectandri n
B whi ch is admi ni stered i n a pharmaceuti cal composition
compri si ng adjuvants , carri ers and di luents and wherei n the
composition i s to be admi ni stered oral ly or parenteral ly.

6. c laims: 1-10, 15, 16, 18-21 (al 1 parti al ly)

Methods for attenuati ng prol iferati on of a Pl asmodi um
organi sm or for attenuati ng prol iferati on of a Pl asmodi um
organi sm i n a host cel l or i n an i ndi vi dual , or for treati ng
a Pl asmodi um i nfecti on i n an i ndi vi dual compri si ng contacti ng
the organi sm, or the host cel l or the i ndi vi dual with an
effecti ve amount of a 5' AMP-acti vated protei n kinase (AMPK)
acti vati ng agent, wherei n the acti vati ng agent i s obovatol
whi ch is admi ni stered i n a pharmaceuti cal composition
compri si ng adjuvants , carri ers and di luents and wherei n the
composition i s to be admi ni stered oral ly or parenteral ly.

7. c laims: 1-10, 15, 16, 18-21 (al 1 parti al ly)

Methods for attenuati ng prol iferati on of a Pl asmodi um
organi sm or for attenuati ng prol iferati on of a Pl asmodi um
organi sm i n a host cel l or i n an i ndi vi dual , or for treati ng
a Pl asmodi um i nfecti on i n an i ndi vi dual compri si ng contacti ng
the organi sm, or the host cel l or the i ndi vi dual with an
effecti ve amount of a 5' AMP-acti vated protei n kinase (AMPK)
acti vati ng agent, wherei n the acti vati ng agent i s gl abri di n
whi ch is admi ni stered i n a pharmaceuti cal composition
compri si ng adjuvants , carri ers and di luents and wherei n the
composition i s to be admi ni stered oral ly or parenteral ly.

8. c laims: 1-10, 15, 16, 18-21 (al 1 parti al ly)

Methods for attenuati ng prol iferati on of a Pl asmodi um
organi sm or for attenuati ng prol iferati on of a Pl asmodi um
organi sm i n a host cel l or i n an i ndi vi dual , or for treati ng
a Plasmodium infection in an individual comprising containing the organ(s) or the host cell or the individual with an effect of an amount of a 5' AMP-activated kinase (AMPK) activator agent, wherein the activator agent is quercetin which is administered in a pharmaceutical composition comprising adjuvants, carriers and diluents and wherein the composition is to be administered orally or parenterally.

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9. Claims: 1-10, 15, 16, 18-21 (all partially)

Methods for attenuating proliferation of a Plasmodium organ(s) or for attenuating proliferation on of a Plasmodium in a host cell or in an individual, or for treating a Plasmodium infection in an individual comprising containing the organ(s) or the host cell or the individual with an effect of an amount of a 5' AMP-activated kinase (AMPK) activator agent, wherein the activator agent is curcumin which is administered in a pharmaceutical composition comprising adjuvants, carriers and diluents and wherein the composition is to be administered orally or parenterally.

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10. Claims: 1-10, 15, 16, 18-21 (all partially)

Methods for attenuating proliferation on of a Plasmodium organ(s) or for attenuating proliferation on of a Plasmodium in a host cell or in an individual, or for treating a Plasmodium infection in an individual comprising containing the organ(s) or the host cell or the individual with an effect of an amount of a 5' AMP-activated kinase (AMPK) activator agent, wherein the activator agent is berberine which is administered in a pharmaceutical composition comprising adjuvants, carriers and diluents and wherein the composition is to be administered orally or parenterally.

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11. Claims: 1-10, 15, 16, 18-21 (all partially)

Methods for attenuating proliferation on of a Plasmodium organ(s) or for attenuating proliferation on of a Plasmodium in a host cell or in an individual, or for treating a Plasmodium infection in an individual comprising containing the organ(s) or the host cell or the individual with an effect of an amount of a 5' AMP-activated kinase (AMPK) activator agent, wherein the activator agent is epigallocatechin gallate which is administered in a pharmaceutical composition comprising adjuvants, carriers and diluents and wherein the composition is to be administered orally or parenterally.

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12. Claims: 1-10, 15, 16, 18-21 (all partially)

Methods for attenuating proliferation on of a Plasmodium...
organism(s) or for attenuating proliferative on of a Plasmodium or
organism(s) in a host cell or in an individual, or for treating a
Plasmodium in infecting one in an individual comprising contacting
the organism(s), or the host cell or the individual with an
effectiveness amount of a 5' AMP-activated protein kinase (AMPK)
activating agent, wherein the activating agent is the afrole which is administered in a pharmaceutical composition comprising adjuvants, carriers and diluents and wherein the composition is to be administered orally or parenterally.

13. Claims: 1-10, 15, 16, 18-21 (all partially)

Methods for attenuating proliferative on of a Plasmodium or
organism(s) in a host cell or in an individual, or for treating a
Plasmodium in infecting one in an individual comprising contacting
the organism(s), or the host cell or the individual with an
effectiveness amount of a 5' AMP-activated protein kinase (AMPK)
activating agent, wherein the activating agent is the afrole which is administered in a pharmaceutical composition comprising adjuvants, carriers and diluents and wherein the composition is to be administered orally or parenterally.

14. Claims: 1-9, 16, 18-21 (all partially)

Methods for attenuating proliferative on of a Plasmodium or
organism(s) in a host cell or in an individual, or for treating a
Plasmodium in infecting one in an individual comprising contacting
the organism(s), or the host cell or the individual with an
effectiveness amount of a 5' AMP-activated protein kinase (AMPK)
activating agent, wherein the activating agent is the nootkatone which is administered in a pharmaceutical composition comprising adjuvants, carriers and diluents and wherein the composition is to be administered orally or parenterally.

15. Claims: 1-9, 16, 18-21 (all partially)

Methods for attenuating proliferative on of a Plasmodium or
organism(s) in a host cell or in an individual, or for treating a
Plasmodium in infecting one in an individual comprising contacting
the organism(s), or the host cell or the individual with an
effectiveness amount of a 5' AMP-activated protein kinase (AMPK)
activating agent, wherein the activating agent is the cucurbitane tri terpenoids / momordicosides which is administered in a pharmaceutical composition comprising adjuvants, carriers and diluents and wherein the composition is to be administered orally or parenterally.
16. Claims: 1-9, 16, 18-21 (all partially)

Methods for attenuating proliferation of a Plasmodium organism in a host cell or in an individual, or for treating a Plasmodium infection in an individual comprising contacting the organism, or the host cell or the individual with an effect, at the amount of a 5'-AMP-activated protein kinase (AMPK) activating agent, wherein the activating agent is damulin B which is administered in a pharmaceutical composition comprising adjuvants, carriers, and diluents and wherein the composition is to be administered orally or parenterally.

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17. Claims: 1-9, 16, 18-21 (all partially)

Methods for attenuating proliferation of a Plasmodium organism or for attenuating proliferation of a Plasmodium organism in a host cell or in an individual, or for treating a Plasmodium infection in an individual comprising contacting the organism, or the host cell or the individual with an effect, at the amount of a 5'-AMP-activated protein kinase (AMPK) activating agent, wherein the activating agent is a ginsenoside which is administered in a pharmaceutical composition comprising adjuvants, carriers, and diluents and wherein the composition is to be administered orally or parenterally.

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### INTERNATIONAL SEARCH REPORT

**Information on patent family members**

**International application No:** PCT/IB2016/001523

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