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Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

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))*

(54) **Title:** METHODS FOR SCREENING NOVEL CORONAVIRUS ANTIVIRALS AND METHODS OF USING ANTIVIRALS FOR THE TREATMENT OF CORONAVIRUS INFECTIONS

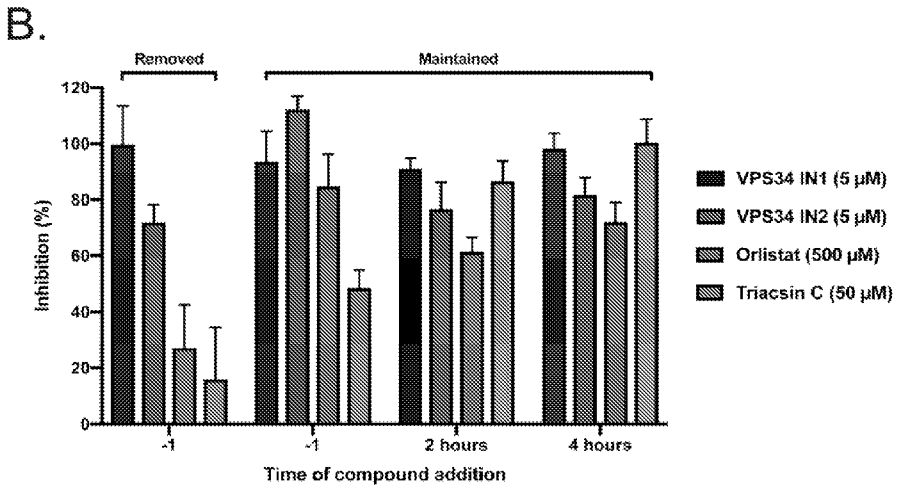

FIG. 4B

(57) **Abstract:** Disclosed are methods for screening for therapeutic agents that can inhibit a coronavirus infection and methods of using agents identified by said assays to treat a coronavirus infection.

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[Continued on next page]

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24 February 2022 (24.02.2022)

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/56; A61K 31/575; A61K 38/21 (2021.01)

CPC - A61K 31/56; A61K 31/575; A61K 38/212; A61K 45/06

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Wei et al., "SNX8 modulates innate immune response to DNA virus by mediating trafficking and activation of MITA" 15 October 2018 (15.10.2018) entire document especially Page 10, Para 2	1-4
X	Hitakarun et al., "Evaluation of the antiviral activity of orlistat (tetrahydrolipstatin) against dengue virus, Japanese encephalitis virus, Zika virus and chikungunya virus" 30 January 2020 (30.01.2020) entire document especially Page 3, Para 4	1, 5, and 6
X	Spencer et al., "Human Cytomegalovirus Induces the Activity and Expression of Acetyl-Coenzyme A Carboxylase, a Fatty Acid Biosynthetic Enzyme Whose Inhibition Attenuates Viral Replication" 19 May 2011 (19.05.2011) entire document especially Page 5819, Para 3	1 and 7
X --- Y	Greseth et al., "De novo Fatty Acid Biosynthesis Contributes Significantly to Establishment of a Bioenergetically Favorable Environment for Vaccinia Virus Infection" 20 March 2014 (20.03.2014) entire document especially Page 3, Para 4; Page 3, Para 5	1, 8, 11 and 14 --- 13
X	Chen et al., "Metabolic reprogramming by Zika virus provokes inflammation in human placenta" 11 June 2020 (11.06.2020) entire document especially Page 5, Para 6 and Page 6, Para 2	1 and 9
X	Narayanan et al., "Distinct Roles for Intracellular and Extracellular Lipids in Hepatitis C Virus Infection" 09 June 2016 (09.06.2016) entire document	1, 10, and 12
Y	US 2011/0256232 A1 (Nygaard et al.) 20 October 2011 (20.10.2011) entire document especially Para [0205]; Para [0315]	13

☒ 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
"D" document cited by the applicant in the international application
"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; 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	Date of mailing of the international search report
16 September 2021 (16.09.2021)	JAN 20 2022
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. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

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International application No.
PCT/US 21/41584

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2015/0098926 A1 (The J. David Gladstone Institutes) 09 April 2015 (09.04.2015) entire document	1-14
A	US 2010/0081713 A1 (Sharma et al.) 01 April 2010 (01.04.2010) entire document	1-14
A	US 2019/0350934 A1 (Cyrano Therapeutics , Inc.) 21 November 2019 (21.11.2019) entire document	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/41584

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.: 18-25
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:

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 searched, the appropriate additional search fees must be paid.

Group I: Claims 1-14, directed to a method of treating a viral infection in a subject comprising administering to the subject an inhibitor of PI3K, an inhibitor of lipases and/or fatty acid synthase, an inhibitor of fatty acyl- CoA-synthetases (ACS), an inhibitor of diacylglyceroi acyltransferase I (DGATI), a palmitoyl acyltransferases (PAT) inhibitor, and/or an inhibitor of fatty acyl-CoA-carboxylases (ACC).

******** Continued on 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.:
1-14

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.

Box III Continued

Group II: Claims 15-17, directed to a method of screening for a therapeutic agent for the treatment, inhibition, reduction, amelioration, and/or prevention of a viral infection the method comprising contacting a monolayer of cells with the therapeutic agent; infecting the monolayer of cells with the virus creating an infected cell monolayer; incubating the infected cell monolayer; and measuring impedance across the monolayer; wherein a decrease in the impedance indicates viral growth, and wherein the impedance at which 50% of the monolayer cells are dead is the 50% inhibitor concentration (IC50), thereby indicating that the therapeutic agent treats, inhibits, reduces ameliorates, and/or prevents viral infection.

Group III: Claims 26-37, directed to a method of inhibiting viral replication comprising contacting a virus with an inhibitor of fatty acid synthesis.

The group of inventions listed above 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:

Special Technical Features:

Group I requires the special technical feature of a method of treating a viral infection in a subject comprising administering to the subject an inhibitor of PI3K, lipases and/or fatty acid synthase, an inhibitor of fatty acyl- CoA-synthetases (ACS), an inhibitor of diacylglyceroi acyltransferase I (DGATI), a palmitoyl acyltransferases (PAT) inhibitor, and/or an inhibitor of fatty acyl-CoA-carboxylases (ACC), not required by Groups II or III.

Group II requires the special technical feature of a method of screening for a therapeutic agent for the treatment, inhibition, reduction, amelioration, and/or prevention of a viral infection the method comprising contacting a monolayer of cells with the therapeutic agent; infecting the monolayer of cells with the virus creating an infected cell monolayer; incubating the infected cell monolayer; and measuring impedance across the monolayer; wherein a decrease in the impedance indicates viral growth, and wherein the impedance at which 50% of the monolayer cells are dead is the 50% inhibitor concentration (IC50), thereby indicating that the therapeutic agent treats, inhibits, reduces ameliorates, and/or prevents viral infection, not required by Groups I and III.

Group III requires the special technical feature of a method of inhibiting viral replication comprising contacting a virus with an inhibitor of fatty acid synthesis, not required by Groups I or II.

Common technical features:

No shared technical features between groups I-III.

Groups I-III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

*Item 4 (contd.): Claims 18-25 determined unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Continued

Group II: Claims 15-17, directed to a method of screening for a therapeutic agent for the treatment, inhibition, reduction, amelioration, and/or prevention of a viral infection the method comprising contacting a monolayer of cells with the therapeutic agent; infecting the monolayer of cells with the virus creating an infected cell monolayer; incubating the infected cell monolayer; and measuring impedance across the monolayer; wherein a decrease in the impedance indicates viral growth, and wherein the impedance at which 50% of the monolayer cells are dead is the 50% inhibitor concentration (IC50), thereby indicating that the therapeutic agent treats, inhibits, reduces ameliorates, and/or prevents viral infection.

Group III: Claims 26-37, directed to a method of inhibiting viral replication comprising contacting a virus with an inhibitor of fatty acid synthesis.

The group of inventions listed above 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:

Special Technical Features:

Group I requires the special technical feature of a method of treating a viral infection in a subject comprising administering to the subject an inhibitor of PI3K, lipases and/or fatty acid synthase, an inhibitor of fatty acyl- CoA-synthetases (ACS), an inhibitor of diacylglyceroi acyltransferase I (DGATI), a palmitoyl acyltransferases (PAT) inhibitor, and/or an inhibitor of fatty acyl-CoA-carboxylases (ACC), not required by Groups II or III.

Group II requires the special technical feature of a method of screening for a therapeutic agent for the treatment, inhibition, reduction, amelioration, and/or prevention of a viral infection the method comprising contacting a monolayer of cells with the therapeutic agent; infecting the monolayer of cells with the virus creating an infected cell monolayer; incubating the infected cell monolayer; and measuring impedance across the monolayer; wherein a decrease in the impedance indicates viral growth, and wherein the impedance at which 50% of the monolayer cells are dead is the 50% inhibitor concentration (IC50), thereby indicating that the therapeutic agent treats, inhibits, reduces ameliorates, and/or prevents viral infection, not required by Groups I and III.

Group III requires the special technical feature of a method of inhibiting viral replication comprising contacting a virus with an inhibitor of fatty acid synthesis, not required by Groups I or II.

Common technical features:

No shared technical features between groups I-III.

Groups I-III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

*Item 4 (contd.): Claims 18-25 determined unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).