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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/761,329	05/04/2020	Jill A LIVENGOOD	271634-488062	5672

114119 7590 08/22/2023

Honigman LLP/ MPI
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER	
CHESTNUT, BARRY A	

ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
08/22/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketing@takeda.com
patents@honigman.com

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APPLICATION NO.	ISSUE DATE	PATENT NO.
16/761,329	22-Aug-2023	11730802

Honigman LLP/ MPI
650 Trade Centre Way
Kalamazoo, MI 49002-0402

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https://patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/761,329	08/22/2023	11730802	271634-488062	5672

114119 7590 08/02/2023

Honigman LLP/ MPI
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 90 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PAIR WEB site http://pair.uspto.gov for additional inventors):

Jill A LIVENGOOD, Cambridge, MA;
Hansi DEAN, Cambridge, MA;
Htay Htay HAN, Cambridge, MA;
Raman RAO, Singapore, SINGAPORE;
Jackie MARKS, Cambridge, MA;

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

TAKEDA VACCINES, INC., Cambridge, MA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

Docket No.: 271634-488062
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Jill A. LIVENGOOD et al.

Application No.: 16/761,329 | Confirmation No.: 5672

Filed: May 4, 2020 | Art Unit: 1648

For: ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME | Examiner: Barry A. CHESTNUT

Via Patent Center
Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF TRANSMISSION UNDER 37 CFR § 1.8(a)

The undersigned hereby certifies that the following documents are being electronically filed in accordance with 37 CFR § 1.6(a)(4), on the 16th day of June, 2023.

1. Part B – Fee Transmittal (1 page); and
2. Certificate of Transmission Under 37 CFR § 1.8(a) (1 page).

/Amy Norris/
Amy Norris
(on behalf of Harold H. Fox, Ph.D., Reg. No. 41,498)

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/761,329	**06/16/2023 03:11:17 PM ET**	**271634-488062**

Title of Invention

ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	5672	FILED BY	Amy Norris
PATENT CENTER #	62287553	FILING DATE	05/04/2020
CUSTOMER #	114119	FIRST NAMED INVENTOR	Jill A LIVENGOOD
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Harold Fox

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
271634-488062_IssueFeeTransmittal.PDF	1	Issue Fee Payment (PTO-85B)	144 KB
271634-488062_CertificateOfTransmission.pdf	1	Miscellaneous Incoming Letter	125 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)

271634-488062_IssueFeeTransmittal.PDF	FD66FB14F5D0AB97E7D04A7B5FCC0D58F367D8C89C22BF6BCE2517AA1413369EB52688E7E181F2F188E9F2743F06555B6F520EA02CAB4886C57C51CBF5966381
271634-488062_CertificateOfTransmission.pdf	8EB8AF836E325695704471FA9026F3B3EE9002988E27B5C54AC283A0D749D2B92A1813FCAAD60CCAEA20C76C493291B82059C877A97E40542950220592AE1322

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

114119 7590 05/31/2023
Honigman LLP/ MPI
650 Trade Centre Way
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Kalamazoo, MI 49002-0402

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Amy Norris	(Typed or printed name)
/Amy Norris/	(Signature)
June 16, 2023	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/761,329	05/04/2020	Jill A LIVENGOOD	271634-488062	5672

TITLE OF INVENTION: ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	08/31/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHESTNUT, BARRY A	1648	424-186100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Honigman LLP
2 Harold H. Fox, Ph.D.
3 Jonathan P. O'Brien, Ph.D.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Takeda Vaccines, Inc.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Cambridge, MA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ☒ Corporation or other private group entity ❑ Government

4a. Fees submitted: ☒ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via Patent Center or EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 50-3145

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Harold H. Fox, Reg. # 41,498/ Date June 16, 2023

Typed or printed name Harold H. Fox, Ph.D. Registration No. 41,498

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United States Patent and Trademark Office
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NOTICE OF ALLOWANCE AND FEE(S) DUE

114119 7590 05/31/2023

Honigman LLP/ MPI
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER
CHESTNUT, BARRY A

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 05/31/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/761,329	05/04/2020	Jill A LIVENGOOD	271634-488062	5672

TITLE OF INVENTION: ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	08/31/2023

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

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114119 7590 05/31/2023
Honigman LLP/ MPI
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Kalamazoo, MI 49002-0402

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Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/761,329	05/04/2020	Jill A LIVENGOOD	271634-488062	5672

TITLE OF INVENTION: ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	08/31/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHESTNUT, BARRY A	1648	424-186100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via Patent Center or EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/761,329	05/04/2020	Jill A LIVENGOOD	271634-488062	5672

114119 7590 05/31/2023

Honigman LLP/ MPI
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER	
CHESTNUT, BARRY A	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 05/31/2023

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/761,329	Applicant(s) LIVENGOOD et al.	
	Examiner Barry Chestnut	Art Unit 1648	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 03/13/2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☑ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 05/12/2023.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/BARRY A CHESTNUT/
Primary Examiner, Art Unit 1648

Continuation of 3. The allowed claim(s) is/are: 65-69,71-99 and 101-133

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 05/01/2023 has been entered.

Priority

This is a National Phase Application filed under 35 U.S.C. 371 as a national stage of PCT/US2018/059233, filed November 5, 2018, an application claiming the benefit of U.S. Provisional Application No. 62/581,500, filed November 3, 2017 and U.S. Provisional Application No. 62/592,995, filed November 30, 2017 that is hereby acknowledged by the Examiner.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 05/12/2023 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement(s) is/are being considered by the Examiner.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Barry Chestnut whose telephone number is 571-270-3546. The examiner can normally be reached on M-F 8 am-4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner' s supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BARRY A CHESTNUT/
Primary Examiner, Art Unit 1648

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16761329
Filing Date	2020-05-04
First Named Inventor	LIVENGOOD, Jill
Art Unit	1648
Examiner Name	CHESTNUT, Barry A.
Attorney Docket Number	271634-488062

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	1	20170298119	A1	2017-10-19	WOLLACOTT et al.	
	2	20190298818	A1	2019-10-03	KINNEY	
	3	20100310656	A1	2010-12-09	BOURINBAIAR et al.	

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	1	2013132040	WO	A2	2013-09-12	NOVARTIS AG		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	2	2017218339	WO	A1	2017-12-21	US HEALTH DEPT OF HHS		
	3	2019042555	WO	A1	2019-03-07	HUMABS BIOMED SA		
	4	2019043166	WO	A1	2019-03-07	HUMABS BIO MED SA		
	5	2020087038	WO	A1	2020-04-30	NY BLOOD CENTER INC, UNIV OF MINNESOTA		
	6	2020106358	WO	A1	2020-05-08	TAKEDA VACCINES, INC.		
	7	2021262659	WO	A1	2021-12-30	UNIV OF CONNECTICUT		
	8	2019172982	WO	A1	2019-09-12	CODAGENIX INC.		
	9	2018237039	WO	A1	2018-12-27	UNIV. TEXAS TECH SYSTEM		
	10	107188935	CN	A	2017-09-22	BEIJING GENESEE BIOLOGICAL TECH CO LTD.		☒
	11	107406856	CN	A	2017-11-28	TAKEDA VACCINES, INC.		☒

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1	ANDRADE, D. et al., "Recent advances in understanding the adaptive immune response to Zika virus and the effect of previous flavivirus exposure", VIRUS RESEARCH, Vol. 254, 26 June 2017 (2017-06-26), page 27-33.	
	2	Anonymous, "Native Antigen Company - Certificate of Analysis - Zika Virus VLP (E, prM/M Proteins)", 30 April 2019 (2019-04-30), Retrieved from the Internet: URL:https://thenativeantigencompany.com/wp-content/uploads/2018/10/CofA-ZIKV-VLP-100-Batch17061910-new-address.pdf	
	3	Anonymous, "A Study of Purified Inactivated Ziak Virus Vaccine (PIZV) in Healthy Adults," July 22, 2022. ClinicalTrials.gov.	
	4	COSENTINO, G., "AlphaLISA Assays to Improve the Vaccine Development Process", 01 January 2011 (2011-01-01), Potency Testing of Veterinary Vaccines for Animals, 134, pages 107-111.	
	5	GARG, H. et al., "Development of Virus-Like-Particle Vaccine and Reporter Assay for Zika Virus", JOURNAL OF VIROLOGY, Vol. 91, No. 20, 15 October 2017 (2017-10-15).	
	6	HASAN, S. et al., "A human antibody against Zika virus crosslinks the E protein to prevent infection", NATURE COMMUNICATIONS, Vol. 8, 16 March 2017 (2017-03-16), page 14722.	
	7	International Search Report for PCT/US2022/015821, mailed on 28 September 2022	
	8	KHANDIA, R. et al., "Modulation of Dengue/Zika Virus Pathogenicity by Antibody-Dependent Enhancement and Strategies to Protect Against Enhancement in Zika Virus Infection", FRONTIERS IN IMMUNOLOGY, Vol. 9, 23 April 2018 (2018-04-23).	
	9	LECOUTURIER, V., et al. "Immunogenicity and Protection Conferred by an Optimized Purified Inactivated Zika Vaccine in Mice," Vaccine, Vol. 37, No 20, May 6, 2019.	
	10	OPALKA, D. et al., "Simultaneous quantitation of antibodies to neutralizing epitopes on virus-like particles for human papillomavirus types 6, 11, 16, and 18 by a multiplexed luminex assay", CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, AMERICAN SOCIETY FOR MICROBIOLOGY, US, Vol. 10, No. 1, 01 January 2003 (2003-01-01), page 108-115.	

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	11	RICHNER, J. et al., "Zika virus vaccines: immune response, current status, and future challenges", CURRENT OPINION IN IMMUNOLOGY, ELSEVIER, OXFORD, GB, Vol. 53, 10 May 2018 (2018-05-10), page 130-136.	
	12	JIANG, S. et al., "Advances in the research and development of therapeutic antibodies against the Zika virus", 25 May 2018 (2018-05-25), Vol. 16, No. 1, page 96-97.	
	13	WANG, H. et al., "The establishment and clinical evaluation of a novel, rapid, no-wash one-step immunoassay for the detection of dengue virus non-structural protein 1", 30 November 2019 (2019-11-30), J Vir Meth Vol. 276, 113793.	
	14	Written Opinion of the International Searching Authority for PCT/US2022/015821, mailed on 28 September 2022.	
	15	YANLING, W. et al., "Neutralization of Zika virus by germline-like human monoclonal antibodies targeting cryptic epitopes on envelope domain III", EMERGING MICROBES & INFECTIONS, Vol. 6, No. 10, 11 October 2017 (2017-10-11), page 1-11.	
	16	Deqiao TIAN, Wei CHEN, Research on Zika Viruses and Vaccines Thereof, Chinese Journal of Biotechnology, Vol.33, No.1, Pages 1-15, January 25 2017.	
	17	LIMA, T. et al., "Purification of flavivirus VLPs by a two-step chomatographic process", 11 June 2019 (2019-06-11), Vol. 37, No. 47, page 7061-7069.	
	18	Live Attenuated Vaccines: Reminder to Avoid Use In Immunosuppressed Individuals, Reaksi, National Pharmaceutical Regulatory Agency (NPRA), Malaysia, September 2017, No. 31.	
	19	MONATH, Thomas P. et al., "An Inactivated Cell-Culture Vaccine against Yellow Fever", The New England Journal of Medicine, April 7, 2011, 364, 1326-1333.	
	20	NAKAMURA, N., "BALB/C Mouse," Brenner's Encyclopedia of Genetics, 2nd Edition, Vol. 1, 2013.	
	21	SMITH, T. et al., "An electrochemiluminescence assay for analysis of rabies virus glycoprotein content in rabies vaccines", VACCINE, Vol. 31, No. 33, 2013, page 3333-3338.	

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	Attorney Docket Number	271634-488062

	22	TYPES OF VACCINES https://www.immunue.org.nz/vaccines/vaccine-development/types-vaccines, September 2020.	
	23	WODI, A. Patricia et al., "Principles of Vaccination, Immunology and Vaccine Preventable Diseases", Epidemiology of Vaccine-Preventable Diseases, 14th edition, https://www.cdc.gov/vaccines/pubs/pinkbook/prinvac.html.	
	24	WOODS, Christopher W. et al., "An observer blinded, randomized, Placebo-controlled, phase I dose escalation trial to evaluate the safety and immunogenicity of an inactivated West Nile virus Vaccine, HydroVax-001, in healthy adults", Vaccine, 37, 2019, 4222-4230.	
	25	ZURBIA-FLORES, Gerardo Montalvo et al., "Re-thinking yellow fever vaccines: fighting old foes with new generation vaccines", Human Vaccines & Immunotherapeutics, Volume 18, No. 1, 1895644, DOI: 10.1080/21645515.2021.1895644.	
	26	DJAGBARE, Matieyendou D. et al., "Monocloncal antibody based in vitro potency assay as a predictor of antigenic integrity and in vivo immunogenicity of a Respiratory Syncytial Virus post-fusion F-protein based vaccine", Vaccine, 36, 2018, 1673-1680.	
	27	BURRELL, Christopher et al., "Vaccines and Vaccination", Principles of Vaccinations, Chapter 11, pp. 155-167	
	28	"IXIARO" Summary of Product Characteristics	
	29	"Encepur Erwachsene", Chiron Vaccines package insert, 2005	
	30	HTAY-HTAY, Han et al., "Safety and immunogenicity of a purified inactivated zika virus vaccine candidate in healthy adults: an observer-blind, randomised, phase 1 trial", The Lancet Infectious Diseases, 21(9), 1282-1292	

If you wish to add additional non-patent literature document citation information please click the Add button [Add]

EXAMINER SIGNATURE

Examiner Signature	/BARRY A CHESTNUT/	Date Considered	05/24/2023

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.A.C/

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	Attorney Docket Number	271634-488062

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Art Unit	1648
	Examiner Name	CHESTNUT, Barry A.
	Attorney Docket Number	271634-488062

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox/	Date (YYYY-MM-DD)	2023-05-12
Name/Print	Harold H. Fox, Ph.D.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.A.C/

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.A.C/

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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	16761329	Filing Date	2020-05-04	Docket Number (if applicable)	271634-488062	Art Unit	1648
First Named Inventor	Jill A. Livengood			Examiner Name	Barry A. Chestnut		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☐ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 50-3145

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
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Signature of Registered U.S. Patent Practitioner			
Signature	/Harold H. Fox, Reg. No. 41,498/	Date (YYYY-MM-DD)	2023-05-12
Name	Harold Fox, Ph.D.	Registration Number	41498

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

114119 7590 04/10/2023

Honigman LLP/ MPI
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER
CHESTNUT, BARRY A

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/10/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/761,329	05/04/2020	Jill A LIVENGOOD	271634-488062	5672

TITLE OF INVENTION: ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	07/10/2023

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

114119 7590 04/10/2023
Honigman LLP/ MPI
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/761,329	05/04/2020	Jill A LIVENGOOD	271634-488062	5672

TITLE OF INVENTION: ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	07/10/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHESTNUT, BARRY A	1648	424-186100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via Patent Center or EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/761,329	05/04/2020	Jill A LIVENGOOD	271634-488062	5672

114119 7590 04/10/2023

Honigman LLP/ MPI
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER	
CHESTNUT, BARRY A	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/10/2023

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/761,329	Applicant(s) LIVENGOOD et al.	
	Examiner Barry Chestnut	Art Unit 1648	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 03/13/2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☑ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 03/13/2023.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/BARRY A CHESTNUT/
Primary Examiner, Art Unit 1648

Continuation of 3. The allowed claim(s) is/are: 65-69,71-99 and 101-133

Notice of References Cited	Application/Control No. 16/761,329	Applicant(s)/Patent Under Reexamination LIVENGOOD et al.	
	Examiner Barry Chestnut	Art Unit 1648	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	NONE CITED.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16761329
Filing Date	2020-05-04
First Named Inventor	Jill A. LIVENGOOD
Art Unit	1648
Examiner Name	Chestnut, Barry A
Attorney Docket Number	271634-488062

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	11219681	B2	2022-01-11	VALNEVA AUSTRIA GMBH	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20100310656	A1	2010-12-09	IMMUNITOR USA INC	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	15202585.4	EP	A1	2017-06-29	Valneva SE		
	2	16161068.8	EP	A1	2017-06-29	Valneva SE		
	3	16176025.1	EP	A1	2017-06-29	Valneva SE		

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.A.C/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16761329
	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	1648
	Examiner Name	Chestnut, Barry A
	Attorney Docket Number	271634-488062

	4	16176049.1	EP	A1	2017-06-29	Valneva SE		
	5	16182845.4	EP	A1	2017-06-29	Valneva SE		
	6	2020524598	JP	A	2020-08-20	EPPENDORF AG		
	7	2012160199	WO	A1	2012-11-29	GLAXOSMITHKLINE BIOLOG SA		
	8	2017161151	WO	A1	2017-09-21	NOVAVAX INC		
	9	2018237039	WO	A1	2018-12-27	UNIV TEXAS TECH SYSTEM		
	10	2016209805	WO	A1	2016-12-29	HARVARD COLLEGE		

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	ANNUNZIATO, F., et al., "The 3 major types of innate and adaptive cell-mediated effector immunity," Journal of Allergy Clin. Immunology, Vol. 135, No. 3, March 2015.	
	2	AUBRY, F., et al., "Flavivirus reverse genetic systems, construction techniques and applications: A historical perspective," Elsevier, Antiviral Research, Vol. 114, pages 67-85, 12 December 2014.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.A.C/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16761329
	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	1648
	Examiner Name	Chestnut, Barry A
	Attorney Docket Number	271634-488062

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Signature	/Harold H. Fox/	Date (YYYY-MM-DD)	2023-03-13
Name/Print	Harold H. Fox, Ph.D.	Registration Number	41,498

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	41	WOODS, Christopher W. et al., "An observer blinded, randomized, Placebo-controlled, phase I dose escalation trial to evaluate the safety and immunogenicity of an inactivated West Nile virus Vaccine, HydroVax-001, in healthy adults", Vaccine, 37, 2019, 4222-4230.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16761329
	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	1648
	Examiner Name	Chestnut, Barry A
	Attorney Docket Number	271634-488062

EXAMINER SIGNATURE			
Examiner Signature	/BARRY A CHESTNUT/	Date Considered	04/04/2023

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16761329
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	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	1648
	Examiner Name	Chestnut, Barry A
	Attorney Docket Number	271634-488062

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox/	Date (YYYY-MM-DD)	2023-03-13
Name/Print	Harold H. Fox, Ph.D.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Jill A. LIVENGOOD et al.	
Application No.:16/761,329	Confirmation No.: 5672
Filed: May 4, 2020	Art Unit: 1648
For: ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME	Examiner: Barry A. CHESTNUT

RESPONSE TO NON-FINAL OFFICE ACTION DATED SEPTEMBER 14, 2022 UNDER 37 CFR §1.111

Via Patent Center
MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This communication is responsive to the Non-Final office Action dated September 14, 2022.

Amendments to the Claims are reflected in the listing of claims which begins on page **2** of this paper.

Remarks/Arguments begin on page **13** of this paper.

AMENDMENTS TO THE CLAIMS

The listing of claims will replace all prior versions, and listings, of claims in the application.

LISTING OF CLAIMS:

1-64. (Canceled)

65. (Currently Amended) A method of vaccinating against Zika virus infection in a human subject in need thereof,

the method comprising administering to the human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus as a first (prime) and a second (boost) administration, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of at least 80% in a population of at least 20 Zika virus seronegative subjects.

66. (Previously Presented) The method of claim 65, wherein the subject is pregnant or intends to become pregnant or is a woman of childbearing potential.

67. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.

68. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition is administered one or more times.

69. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition comprising a dose of 10 μg is administered one time.

70. (Cancelled)

71. (Currently Amended) The method of claim [[70]]65, wherein the prime and boost administration takes place from about 1 to about 16 weeks apart or from about 1 to about 6 weeks apart or from about 1 to about 4 weeks apart or from about 3 to about 5 weeks apart.

72. (Currently Amended) The method of claim [[70]]65, wherein the second (boost) administration is administered from about 25 days to about 30 days after the first (prime) administration.

73. (Previously Presented) The method of claim 65, wherein 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 1000, or of greater than 1500, or of greater than 2000, or of greater than 3000 are induced, as determined by the plaque reduction neutralization test (PRNT).

74. (Currently Amended) A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration.

75. (Currently Amended) The method of claim [[70]]65, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of ~~at least 80%, or~~ at least 90%~~, or at least 95%, or 100%~~ in a population of at least 20 Zika virus seronegative subjects.

76. (Currently Amended) ~~The method of claim 68,~~ A method of vaccinating against Zika virus infection in a human subject in need thereof,

the method comprising administering to the human subject a vaccine or immunogenic composition comprising a dose of from about 1 µg to about 40 µg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, wherein the vaccine or immunogenic composition is administered one or more times, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after a single dose or prime administration a seroconversion rate of at least 60%~~, or at least 70%, or at least 80%, or at least 90%~~ in a population of at least 20 Zika virus seronegative subjects.

77. (Currently Amended) The method of claim [[70]]65, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration, geometric mean neutralizing antibody titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects, which are at least 10 times, or at least 15 times, or at least 20 times, or at least 25 times higher than the geometric mean neutralizing antibody titers induced 28 days after the prime administration, as determined by the plaque reduction neutralization test (PRNT).

78. (Previously Presented) The method of claim 65, wherein the antigen is purified.

79. (Previously Presented) The method of claim 78, wherein the main peak of the antigen when analyzed by size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

80. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of from about 10 µg to about 40 µg of purified inactivated whole virus.

81. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of from about 10 µg to about 30 µg of purified inactivated whole virus.

82. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of from about 10 µg to about 20 µg of purified inactivated whole virus.

83. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of about 10 µg to about 15 µg of purified inactivated whole virus.

84. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of about 2 µg, or about 5 µg, or about 10 µg of purified inactivated whole virus.

85. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of about 10 µg of purified inactivated whole virus.

86. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition further comprises an aluminum salt adjuvant.

87. (Previously Presented) The method of claim 86, wherein the vaccine or immunogenic composition comprises from about 100 µg to about 600 µg or from about 100 µg to about 450 µg or from about from about 100 µg to about 300 µg or from about 150 µg to about 250 µg or from about 100 µg to about 225 µg or about 200 µg of an aluminum salt as adjuvant.

88. (Previously Presented) The method of claim 86, wherein the adjuvant is aluminum hydroxide.

89. (Previously Presented) The method of claim 86, wherein at least 75%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or 100% of the antigen are adsorbed to the adjuvant.

90. (Previously Presented) The method of claim 65, wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.

91. (Currently Amended) ~~The method of claim 65~~ A method of vaccinating against Zika virus infection in a human subject in need thereof,

the method comprising administering to the human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg of purified inactivated whole virus, about 200 μg aluminum hydroxide, a buffer; and optionally a sugar ~~such as sucrose~~.

92. (Previously Presented) The method of claim 65, wherein administration of the vaccine or immunogenic composition to the human subject does not result in the subject having a severe adverse event as a result of the administration.

93. (Previously Presented) The method of claim 92, wherein the severe adverse event is a fever of a temperature of 39°C or higher.

94. (Previously Presented) The method of claim 65, wherein the subject is from a Zika endemic region or from a Zika non-endemic region travelling to an endemic region.

95. (Previously Presented) The method of claim 65, wherein the subject is 18 to 29 years of age or 30 to 49 years of age.

96. (Previously Presented) The method of claim 65, wherein the subject is a female subject.

97. (Previously Presented) The method of claim 74, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.

98. (Previously Presented) The method of claim 74, wherein the vaccine or immunogenic composition is administered one or more times.

99. (Previously Presented) The method of claim 74, wherein the vaccine or immunogenic composition comprising a dose of 10 μg is administered one time.

100. (Cancelled)

101. (Currently Amended) The method of claim [[100]] 74, wherein the prime and boost administration takes place from about 1 to about 16 weeks apart or from about 1 to about 6 weeks apart or from about 1 to about 4 weeks apart or from about 3 to about 5 weeks apart.

102. (Currently Amended) The method of claim [[100]] 74, wherein the second (boost) administration is administered from about 25 days to about 30 days after the first (prime) administration.

103. (Currently Amended) The method of claim [[100]] 74, wherein 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in the pregnant human subject of greater than 1000, or of greater than 1500, or of greater than 2000, or of greater than 3000 are induced, as determined by the plaque reduction neutralization test (PRNT).

104. (Currently Amended) The method of claim [[100]] 74, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of at least 80%, or at least 90%, or at least 95%, or 100% in a population of at least 20 Zika virus seronegative subjects.

105. (Currently Amended) The method of claim [[100]] 74, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after a single dose or prime administration a seroconversion rate of at least 60%~~, or at least 70%, or at least 80%, or at least 90%~~ in a population of at least 20 Zika virus seronegative subjects.

106. (Currently Amended) The method of claim [[100]] 74, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration, geometric mean neutralizing antibody titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects, which are at least 10 times, or at least 15 times, or at least 20 times, or at least 25 times higher than the geometric mean neutralizing antibody titers induced 28 days after the prime administration, as determined by the plaque reduction neutralization test (PRNT).

107. (Currently Amended) A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 µg to about 40 µg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn~~The method of claim 74~~, wherein the antigen is purified.

108. (Previously Presented) The method of claim 107, wherein the main peak of the antigen when analyzed by size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

109. (Currently Amended) ~~The method of claim 74~~A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 µg to about 40 µg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, wherein the vaccine or immunogenic

composition comprises a dose of from about 10 μg to about 40 μg of purified inactivated whole virus.

110. (Previously Presented) The method of claim 74, wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 30 μg of purified inactivated whole virus.

111. (Previously Presented) The method of claim 74, wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 20 μg of purified inactivated whole virus.

112. (Previously Presented) The method of claim 74, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg to about 15 μg of purified inactivated whole virus.

113. (Previously Presented) The method of claim 74, wherein the vaccine or immunogenic composition comprises a dose of about 2 μg, or about 5 μg, or about 10 μg of purified inactivated whole virus.

114. (Previously Presented) The method of claim 74, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg of purified inactivated whole virus.

115. (Currently Amended) ~~The method of claim 74~~A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, wherein the vaccine or immunogenic composition further comprises an aluminum salt adjuvant.

116. (Previously Presented) The method of claim 115, wherein the vaccine or immunogenic composition comprises from about 100 μg to about 600 μg or from about 100 μg to about 450 μg or from about from about 100 μg to about 300 μg or from about 150 μg to about 250 μg or from about 100 μg to about 225 μg or about 200 μg of an aluminum salt as adjuvant.

117. (Previously Presented) The method of claim 115, wherein the adjuvant is aluminum hydroxide.

118. (Previously Presented) The method of claim 115, wherein at least 75%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or 100% of the antigen are adsorbed to the adjuvant.

119. (Currently Amended) ~~The method of claim 74~~A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.

120. (Currently Amended) ~~The method of claim 74~~A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg of purified inactivated whole virus, about 200 μg aluminum hydroxide, a buffer; and optionally a sugar ~~such as sucrose~~.

121. (Previously Presented) The method of claim 74, wherein administration of the vaccine or immunogenic composition to the pregnant human subject does not result in the pregnant human subject having a severe adverse event as a result of the administration.

122. (Previously Presented) The method of claim 121, wherein the severe adverse event is a fever of a temperature of 39°C or higher.

123. (Previously Presented) ~~The method of claim 74~~A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 µg to about 40 µg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, wherein the pregnant human subject is from a Zika endemic region or from a Zika non-endemic region travelling to an endemic region.

124. (Currently Amended) ~~The method of claim 74~~A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 µg to about 40 µg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn, wherein the pregnant human subject is 18 to 29 years of age or 30 to 49 years of age.

125. (New) The method of claim 65, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of at least 95% or 100%.

126. (New) The method of claim 76, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 80% in a population of at least 20 Zika virus seronegative subjects.

127. (New) The method of claim 76, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 90% in a population of at least 20 Zika virus seronegative subjects.

128. (New) The method of claim 76, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 95% in a population of at least 20 Zika virus seronegative subjects.

129. (New) The method of claim 91, wherein the sugar is sucrose.

130. (New) The method of claim 120, wherein the sugar is sucrose.

131. (New) The method of claim 105, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 70% in a population of at least 20 Zika virus seronegative subjects.

132. (New) The method of claim 105, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 80% in a population of at least 20 Zika virus seronegative subjects.

133. (New) The method of claim 105, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 90% in a population of at least 20 Zika virus seronegative subjects.

REMARKS

Status of the Claims

Claims 65, 71, 72, 74-77, 91, 101-107, 109, 115, 119, 120, 123, 1and 24 are currently amended. Claims 125-133 are new. Claims 70 and 100 are cancelled without prejudice. Claims 1-64 were previously canceled. Claims 65-69, 71-99, and 101-133 are currently pending.

The present amendments are supported in the specification and claims as originally filed, including the examples and figures as filed. No new matter has been added.

Applicant reserves the right to file continuation applications or divisional applications as deemed necessary to protect the subject matter restricted, or withdrawn from this application.

Claim Objections

Applicant respectfully thanks the Examiner for the finding of allowable subject matter in claims 75, 76, 77, 97-102, 107-119 and 123-124. The claim amendments presented herein render these claims allowable. Allowance is respectfully requested.

Rejection Under 35 USC §112

Claims 91 and 120 are presently rejected under 35 U.S.C. 112(b), as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 91 and 120 recite the term “such as”. The recitation "such as" in claims 91 and 120 are deemed to render the claims indefinite.

Without acquiescing to the propriety of the present rejection, Applicant has deleted reference to the terms "such as sucrose" in each of claims 91 and 120, thereby rendering the present rejection moot.

The Examiner is respectfully requested to reconsider and withdraw the objection of claims 91 and 120 under 35 U.S.C. §112(b).

Rejection Under 35 USC §102

Claims 65, 66-72, 78, 79, 80-90 and 96 are rejected under 35 U.S.C. 102(a)(1) as allegedly being anticipated by Barbero et al. (WO2017/109223, hereinafter "*Barbero*").

Furthermore, the Office Action states that with respect to claims 65, 66, 69, 78, 79, 80-86, 88-90 and 96, *Barbero* allegedly discloses a Zika virus vaccine (abstract), which is purified (*Barbero* at page 7 lines 9-12), and is inactivated by formalin (page 108 lines 1-5). The Office Action further alleges that *Barbero* discloses the antigen doses of 0.012-12 μg and adjuvanted with $AlOH_3$ (*Barbero* at page 114 lines 1-5) for human trials (*Barbero* at page 115 lines 27-32); and pregnant women (*Barbero* at page 116 lines 13-22).

Regarding claims 67-68, the Office Action alleges that *Barbero* discloses the administration may be intramuscular or subcutaneous one or more times (*Barbero* at page 24 lines 1-7).

Regarding claims 70-72, the Office Action alleges that *Barbero* discloses administration and a second administration (boost) 3-4 weeks later (*Barbero* at page 115 lines 11-25).

Regarding claim 87, the Office Action alleges that *Barbero* discloses administering aluminum hydroxide adjuvant at 500 μg/ml (*Barbero* at page 112 lines 1-5).

Not in acquiescence to these rejections, the claims have been amended to cover the indicated allowable subject matter. Applicant respectfully requests that these rejections be reconsidered and withdrawn.

Rejection Under 35 USC §103

Claims 73-74, 89, 92-93, 94, 95, 103-106, 121-122 are presently rejected under 35 U.S.C. §103(a) as being unpatentable over *Barbero*.

Not in acquiescence to these rejections, the claims have been amended to cover the indicated allowable subject matter. Applicant respectfully requests that these rejections be reconsidered and withdrawn.

CONCLUSION

In view of the remarks above, Applicant believes the pending application is in condition for allowance.

Applicant hereby authorizes the Office to charge the large entity three (3) months of extension of time fee of $1,480.00 and excess claims fees of $4,540.00 to Deposit Account No. 503145, referencing Attorney Docket No. 271634-488062.

It is believed that no fees are required for this submission. However, should there be any charges required to maintain this application in good order, please deduct those charges from Deposit Account No. 50-3145, referencing Attorney Docket No. 271634-488063, and notify the undersigned attorney directly immediately.

Respectfully submitted,

Dated: March 13, 2023

/Harold H. Fox/
Harold H. Fox, Ph.D.
Registration No. 41,498
Honigman LLP
1440 New York Ave., NW, Suite 200
Washington, D.C. 20005
Telephone: 202-844.3380
Email: hofox@honigman.com
Patents@honigman.com

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(Not for submission under 37 CFR 1.99)

Application Number	16761329
Filing Date	2020-05-04
First Named Inventor	Jill A. LIVENGOOD
Art Unit	1648
Examiner Name	Chestnut, Barry A
Attorney Docket Number	271634-488062

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	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	1648
	Examiner Name	Chestnut, Barry A
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16761329
	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	1648
	Examiner Name	Chestnut, Barry A
	Attorney Docket Number	271634-488062

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If you wish to add additional non-patent literature document citation information please click the Add button Add

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Attorney Docket Number	271634-488062

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16761329
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	Examiner Name	Chestnut, Barry A
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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox/	Date (YYYY-MM-DD)	2023-03-13
Name/Print	Harold H. Fox, Ph.D.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/761,329	05/04/2020	Jill A LIVENGOOD	271634-488062	5672

114119 7590 09/14/2022

Honigman LLP/ MPI
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER	
CHESTNUT, BARRY A	

ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
09/14/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketing@takeda.com
patents@honigman.com

Office Action Summary	Application No. 16/761,329	Applicant(s) LIVENGOOD et al.	
	Examiner Barry Chestnut	Art Unit 1648	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 06/28/2022.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 65-124 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 65-124 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 05/04/2020 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 5/4/2020, 6/28/2022, 8/5/2022.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Priority

This application is a National Phase Application filed under 35 U.S.C. 371 as a national stage of PCT/US2018/059233, filed November 5, 2018, an application claiming the benefit of U.S. Provisional Application No. 62/581,500, filed November 3, 2017 and U.S. Provisional Application No. 62/592,995, filed November 30, 2017 that is hereby acknowledged by the Examiner.

Status of the Claims

The amendment dated 06/28/2022 is acknowledged. Claims 65-124 are pending and under examination.

Election/Restrictions

Applicant's election of Group 2 in the reply filed on 06/28/2022 is acknowledged. Election was made without traverse in the reply filed on 06/28/2022. Claim 65-73 of group 2 were elected in the reply filed on 06/28/2022. Claims 74-124 are newly added claims that read on elected group 2.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 5/4/2020, 6/28/2022, 8/5/2022 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement(s) is/are being considered by the Examiner.

Claim Objections

Claims 75, 76, 77, 97-102, 107-119 and 123-124 are objected to for the following informalities:

- Claims 75, 76, 77, 97-102, 107-119 and 123-124 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):

> (B) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

Claims 91 and 120 are rejected under 35 U.S.C. 112(b), as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 91 and 120 recites “such as”. The recitation "such as" in claims 91 and 120 are relative terms which renders the claim indefinite. The term "such as" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus, the claim is rendered indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.
>
> (a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

Claims 65, 66-72, 78, 79, 80-90 and 96 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Barbero et al. “Barbero” (WO2017/109223).

The claims are directed to a method of vaccinating against Zika virus infection in a human subject in need thereof, the method comprising administering to the human subject a vaccine or immunogenic composition comprising a dose of from about 1 ug to about 40 ug of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus.

Regarding claims 65, 66, 69, 78, 79, 80-86, 88-90 and 96, Barbero discloses a Zika virus vaccine (abstract), purified (page 7 lines 9-12), that is inactivated by formalin (page 108 lines 1-5). Barbero discloses the antigen doses of 0.012-12 ug and adjuvanted with $AlOH_3$ (page 114 lines 1-5) for human trials (page 115 lines 27-32); and pregnant women (page 116 lines 13-22).

Regarding claims 67-68, Barbero discloses the administration may be intramuscular or subcutaneous one or more times (page 24 lines 1-7).

Regarding claims 70-72, Barbero discloses administration and a second administration (boost) 3-4 weeks later (page 115 lines 11-25).

Regarding claim 87, Barbero discloses administering aluminum hydroxide adjuvant at 500 ug/ml (page 112 lines 1-5).

Therefore, the cited prior art anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 73-74, 89, 92-93, 94, 95, 103-106, 121-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbero et al. "Barbero" (WO2017/109223).

The teachings of Barbero et al. are outlined above and incorporated herein.

Regarding claims 73-74, Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Regarding claim 89, Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Regarding claims 92-93, Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Regarding claim 94, Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed

protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Regarding claim 95, the age of the subject is not inventive and considered routine and obvious. According to section 2144.05 of the M.P.E.P., "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). It would have been obvious for one of ordinary skill to determine the appropriate age for administration of the composition.

Regarding claims 103-106, Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Regarding claims 121-122, Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Barry Chestnut whose telephone number is (571)270-3546. The examiner can normally be reached on M-Th 8:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BARRY A CHESTNUT/
Primary Examiner, Art Unit 1648

Notice of References Cited	Application/Control No. 16/761,329	Applicant(s)/Patent Under Reexamination LIVENGOOD et al.	
	Examiner Barry Chestnut	Art Unit 1648	Page 1 of 1

U.S. PATENT DOCUMENTS

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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO2017109223	06-2017	WIPO	Barbero et al.	--
	O					
	P					
	Q					
	R					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16761329
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Examiner Name	Barry A. CHESTNUT
Attorney Docket Number	271634-488062

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.A.C/

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	Examiner Name	Barry A. CHESTNUT
	Attorney Docket Number	271634-488062

	1	REAGAN, R. L., et al; "ELECTRON MICROGRAPHS OF ERYTHROCYTES FROM SWISS ALBINO MICE INFECTED WITH ZIKA VIRUS"; From the Virus Laboratory, Live Stock Sani Service, University of Maryland, College Park, Maryland. Received for publication 28 April 1955	
	2	BRETT, U.; "Zika-Virus-Infektionen"; Laboratoriumsmedizin; https://www.mta-dialog.de/artikel/zika-virus-infektionen.html; 1 April 2016	
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	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	1648
	Examiner Name	Barry A. CHESTNUT
	Attorney Docket Number	271634-488062

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Examiner Signature	/BARRY A CHESTNUT/	Date Considered	09/08/2022

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Signature	/Fernando Alberdi/	Date (YYYY-MM-DD)	2022-06-28
Name/Print	Fernando Alberdi, Ph.D.	Registration Number	62,688

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Application Number	
Filing Date	2020-05-04
First Named Inventor	Jill A. LIVENGOOD
Art Unit	~~TBD~~ 1648
Examiner Name	~~TBD~~ /BARRY A CHESTNUT/
Attorney Docket Number	38011U

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	1	2017/009873	WO	A1	2017-01-19	BHARAT BIOTECH INTERNATIONAL LIMITED		
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	First Named Inventor	Jill A. LIVENGOOD
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	1	International Search Report dated March 15, 2019 issued in corresponding Application No. PCT/US2018/059233	
	2	TIWARI, et al., "Assessment of immunogenic potential of Vero adapted formalin inactivated vaccine derived from novel ECSA genotype of Chikungunya virus", Vaccine, Vol. 27, No. 18, pp. 2513-2522, 2009.	
	3	BALDWIN, et al., "Purified Inactivated Zika Vaccine Candidates Afford Protection against Lethal Challenge in Mice", Scientific Reports, Vol. 8, No. 1	
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Signature	/Joshua B. Goldberg/	Date (YYYY-MM-DD)	2020-05-04
Name/Print	Joshua B. Goldberg	Registration Number	44126

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	2	20070110759	A1	2007-05-17	Sattentau et al.	
	3	20170014502	A1	2017-01-19	SUMATHY et al.	
	4	20200360505	A1	2020-11-19	LIVENGOOD et al.	
	5	20210177959	A1	2021-06-17	LIVENGOOD et al.	

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	6	20210106669	A1	2021-04-15	LIVENGOOD et al.	
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	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	1648
	Examiner Name	Barry A. CHESTNUT
	Attorney Docket Number	271634-488062

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Signature	/Fernando Alberdi/	Date (YYYY-MM-DD)	2022-06-28
Name/Print	Fernando Alberdi, Ph.D.	Registration Number	62,688

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	1	102017024030	BR	A2	2019-06-04	Univ Fed Sao Joao Del Rei	English Abstract	
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	4	108503697	CN	A	2018-09-07	Inst Pasteur Shanghai Cas		☒
	5	2010111687	WO	A2	2010-09-30	Academia Sinica		☐
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	15	2017197035	WO	A1	2017-11-16	Najit Technologies, Inc		☐
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Name/Print	Fernando Alberdi, Ph.D.	Registration Number	62,688

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Application Number	16761329
Filing Date	2018-11-05
First Named Inventor	Jill A. LIVENGOOD
Art Unit	1648
Examiner Name	Barry A. CHESTNUT
Attorney Docket Number	271634-488062

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	1	102017024030	BR	A2	2019-06-04	Univ Fed Sao Joao Del Rei	English Abstract	
	2	108210921	CN	A	2018-06-29	Guangzhou Nbiomed Biomedical Tech Co Ltd		☒
	3	108503696	CN	A	2018-09-07	Inst Pasteur Shanghai Cas		☒

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	4	108503697	CN	A	2018-09-07	Inst Pasteur Shanghai Cas		☒
	5	2010111687	WO	A2	2010-09-30	Academia Sinica		☐
	6	2016044023	WO	A1	2016-03-24	Univ Iowa Res Found		☐
	7	2017015463	WO	A2	2017-01-26	Modernatx, Inc		☐
	8	2017056094	WO	A1	2017-04-06	Ramot At Tel-aviv Univ Ltd		☐
	9	2017070624	WO	A1	2017-04-27	Modernatx, Inc		☐
	10	2017109211	WO	A1	2017-06-29	Themis Bioscience GmbH		☐
	11	2017132210	WO	A1	2017-08-03	Iogenetics, LLC		☐
	12	2017140905	WO	A1	2017-08-24	Curevac AG		☐
	13	2017147458	WO	A1	2017-08-31	Univ Pennsylvania		☐
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	15	2017197035	WO	A1	2017-11-16	Najit Technologies, Inc		☐
	16	2017208191	WO	A1	2017-12-07	Glaxosmithkline Biologicals SA		☐
	17	2017212291	WO	A1	2017-12-14	Imp Innovations Ltd		☐
	18	2017214596	WO	A1	2017-12-14	Beth Israel Deaconess Medical Center, Inc		☐
	19	2018007575	WO	A1	2018-01-11	Inserm (institut National De La Santé Et De La Rec		☐
	20	2018020271	WO	A1	2018-02-01	Univ Oxford Innovation Ltd		☐
	21	2018022786	WO	A1	2018-02-01	Univ Washington		☐
	22	2018091540	WO	A1	2018-05-24	Glaxosmithkline Biologicals SA		☐
	23	2018115509	WO	A2	2018-06-28	Expres2ion Biotechnologies Aps		☐
	24	2018165373	WO	A1	2018-09-13	University Of Georgia Research Foundation, Inc		☐
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	26	2019068877	WO	A1	2019-04-11	Univ Leuven Kath		☐
	27	2019104157	WO	A1	2019-05-31	The Univ Of Vermont And State Agricultural College		☐
	28	2019162465	WO	A1	2019-08-29	Nano4 Global, Lda		☐
	29	2019172982	WO	A1	2019-09-12	Codagenix Inc		☐
	30	2019186199	WO	A1	2019-10-03	Emergex Vaccines Holding Ltd		☐
	31	2019209079	WO	A1	2019-10-31	Catholic Univ Korea Ind Academic Cooperation Found		☐
	32	2020017765	WO	A1	2020-01-23	Genematrix Inc		☒
	33	2021141758	WO	A1	2021-07-15	Xu, Jian		☐

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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Signature	/Fernando Alberdi/	Date (YYYY-MM-DD)	2022-08-05
Name/Print	Fernando Alberdi, Ph.D.	Registration Number	62,688

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	1	REAGAN, R. L., et al; "ELECTRON MICROGRAPHS OF ERYTHROCYTES FROM SWISS ALBINO MICE INFECTED WITH ZIKA VIRUS"; From the Virus Laboratory, Live Stock Sani Service, University of Maryland, College Park, Maryland. Received for publication 28 April 1955	
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☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Fernando Alberdi/	Date (YYYY-MM-DD)	2022-06-28
Name/Print	Fernando Alberdi, Ph.D.	Registration Number	62,688

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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HONIGMAN

Fernando Alberdi, Ph.D.
Office: 734.418.4264
falberdi@honigman.com

Via EFS

June 28, 2022

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313

Re: Application No.: 16/761,329
PCT Filing Date: May 4, 2020
Inventor(s): Jill A. LIVENGOOD et al.
Title: ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME
Confirmation No.: 5672
Attorney Docket No.: 271634-488062

Dear Sir,

Enclosed for filing please find the following documents:

1. Cover Letter to the Commissioner for Patents (2 pages);
2. Response to Restriction Requirement Dated February 28, 2022 (11 pages);
3. Information Disclosure Statement (PTO/SB/08) (26 pages);
4. 26 Foreign References and 141 Non-patent Literature References;
5. Petition for Extension of Time Under 37 CFR 1.136(a) (1 page); and
6. Certificate of Transmission Under 37 CFR §1.8(a) (1 page).

Please charge Deposit Account No. 503145 for $4,640.00, reflecting the payment of $4,000.00 for 40 excess claims over 20, and $640.00 for a two-month extension of time, referencing Attorney Docket Number 271634-488062.

It is believed that no other fees are due at this time. However, if there are any additional charges or credits in direct relation to this filing please charge to Deposit Account No. 503145, referencing Attorney Docket No. 271634-488062, and inform the undersigned attorney directly immediately.

43933255.2

Thank you for your assistance.

Very truly yours,

HONIGMAN LLP

/ Fernando Alberdi /

Fernando Alberdi, Ph.D.

Enclosures

Docket No.: 271634-488062
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Jill A. LIVENGOOD et al.

Application No.:16/761,329 | Confirmation No.: 5672

Filed: May 4, 2020 | Art Unit: 1648

For: ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME | Examiner: Barry A. CHESTNUT

RESPONSE TO RESTRICTION REQUIREMENT DATED FEBRUARY 28, 2022

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This communication is responsive to the Restriction Requirement dated February 28, 2022.

Amendments to the Claims are reflected in the listing of claims which begins on page **2** of this paper.

Remarks/Arguments begin on page **6** of this paper.

44360442.1

AMENDMENTS TO THE CLAIMS

The listing of claims will replace all prior versions, and listings, of claims in the application.

LISTING OF CLAIMS:

Claims 1-64. (Canceled)

65. (Currently Amended) A method of ~~treating or preventing, in particular preventing~~ vaccinating against Zika virus infection in a human subject in need thereof,

the method comprising administering to the human subject ~~the~~ a vaccine or immunogenic composition ~~of claim 55~~ comprising a dose of from about 1 µg to about 40 µg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus.

66. (Currently Amended) The method of ~~any one of~~ claim 65, wherein the subject is pregnant or intends to become pregnant or is a woman of childbearing potential.

67. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.

68. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition is administered one or more times.

69. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition comprising a dose of 10 µg is administered one time.

70. (Previously Presented) The method of claim 65, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration.

71. (Currently Amended) The method of claim 70, wherein the prime and boost administration takes place from about 1 to about 16 weeks apart or from about 1 to about 6 weeks apart or from about 1 to about 4 weeks apart or from about 3 to about 5 weeks apart.

72. (Currently Amended) The method of claim 70, wherein the second (boost) administration is administered ~~at least 28~~ from about 25 days to about 30 days after the first (prime) administration.

73. (Currently Amended) The method of claim 70, wherein 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the generation of neutralizing antibody titers to Zika virus in a subject of greater than 1000, or of greater than 1500, or of greater than 2000, or of greater than 3000 are induced, as determined by the plaque reduction neutralization test (PRNT).

74. (New) A method of vaccinating against Zika virus disease in a fetus or newborn in need thereof, the method comprising administering to a pregnant human subject a vaccine or immunogenic composition comprising a dose of from about 1 μg to about 40 μg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, and wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn.

75. (New) The method of claim 70, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of at least 80%, or at least 90%, or at least 95%, or 100% in a population of at least 20 Zika virus seronegative subjects.

76. (New) The method of claim 68, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after a single dose or prime administration a seroconversion rate of at least 60%, or at least 70%, or at least 80%, or at least 90% in a population of at least 20 Zika virus seronegative subjects.

77. (New) The method of claim 70, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration, geometric mean neutralizing antibody titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus

seronegative subjects, which are at least 10 times, or at least 15 times, or at least 20 times, or at least 25 times higher than the geometric mean neutralizing antibody titers induced 28 days after the prime administration, as determined by the plaque reduction neutralization test (PRNT).

78. (New) The method of claim 65, wherein the antigen is purified.

79. (New) The method of claim 78, wherein the main peak of the antigen when analyzed by size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

80. (New) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 40 μg of purified inactivated whole virus.

81. (New) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 30 μg of purified inactivated whole virus.

82. (New) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 20 μg of purified inactivated whole virus.

83. (New) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg to about 15 μg of purified inactivated whole virus.

84. (New) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of about 2 μg, or about 5 μg, or about 10 μg of purified inactivated whole virus.

85. (New) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg of purified inactivated whole virus.

86. (New) The method of claim 65, wherein the vaccine or immunogenic composition further comprises an aluminum salt adjuvant.

87. (New) The method of claim 86, wherein the vaccine or immunogenic composition comprises from about 100 μg to about 600 μg or from about 100 μg to about 450 μg or from about from about 100 μg to about 300 μg or from about 150 μg to about 250 μg or from about 100 μg to about 225 μg or about 200 μg of an aluminum salt as adjuvant.

88. (New) The method of claim 86, wherein the adjuvant is aluminum hydroxide.

89. (New) The method of claim 86, wherein at least 75%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or 100% of the antigen are adsorbed to the adjuvant.

90. (New) The method of claim 65, wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.

91. (New) The method of claim 65, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg of purified inactivated whole virus, about 200 μg aluminum hydroxide, a buffer; and optionally a sugar such as sucrose.

92. (New) The method of claim 65, wherein administration of the vaccine or immunogenic composition to the human subject does not result in the subject having a severe adverse event as a result of the administration.

93. (New) The method of claim 92, wherein the severe adverse event is a fever of a temperature of 39°C or higher.

94. (New) The method of claim 65, wherein the subject is from a Zika endemic region or from a Zika non-endemic region travelling to an endemic region.

95. (New) The method of claim 65, wherein the subject is 18 to 29 years of age or 30 to 49 years of age.

96. (New) The method of claim 65, wherein the subject is a female subject.

97. (New) The method of claim 74, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.

98. (New) The method of claim 74, wherein the vaccine or immunogenic composition is administered one or more times.

99. (New) The method of claim 74, wherein the vaccine or immunogenic composition comprising a dose of 10 μg is administered one time.

100. (New) The method of claim 74, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration.

101. (New) The method of claim 100, wherein the prime and boost administration takes place from about 1 to about 16 weeks apart or from about 1 to about 6 weeks apart or from about 1 to about 4 weeks apart or from about 3 to about 5 weeks apart.

102. (New) The method of claim 100, wherein the second (boost) administration is administered from about 25 days to about 30 days after the first (prime) administration.

103. (New) The method of claim 100, wherein 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the generation of neutralizing antibody titers to Zika virus in the pregnant human subject of greater than 1000, or of greater than 1500, or of greater than 2000, or of greater than 3000 are induced, as determined by the plaque reduction neutralization test (PRNT).

104. (New) The method of claim 100, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of at least 80%, or at least 90%, or at least 95%, or 100% in a population of at least 20 Zika virus seronegative subjects.

105. (New) The method of claim 98, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after a single dose or prime administration a seroconversion rate of at least 60%, or at least 70%, or at least 80%, or at least 90% in a population of at least 20 Zika virus seronegative subjects.

106. (New) The method of claim 100, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration, geometric mean neutralizing antibody titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects, which are at least 10 times, or at least 15 times, or at least 20 times, or at least 25 times higher than the geometric mean neutralizing antibody titers induced 28 days after the prime administration, as determined by the plaque reduction neutralization test (PRNT).

107. (New) The method of claim 74, wherein the antigen is purified.

108. (New) The method of claim 107, wherein the main peak of the antigen when analyzed by size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

109. (New) The method of claim 74, wherein the vaccine or immunogenic composition comprises a dose of from about 10 µg to about 40 µg of purified inactivated whole virus.

110. (New) The method of claim 74, wherein the vaccine or immunogenic composition comprises a dose of from about 10 µg to about 30 µg of purified inactivated whole virus.

111. (New) The method of claim 74, wherein the vaccine or immunogenic composition comprises a dose of from about 10 μg to about 20 μg of purified inactivated whole virus.

112. (New) The method of claim 74, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg to about 15 μg of purified inactivated whole virus.

113. (New) The method of claim 74, wherein the vaccine or immunogenic composition comprises a dose of about 2 μg, or about 5 μg, or about 10 μg of purified inactivated whole virus.

114. (New) The method of claim 74, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg of purified inactivated whole virus.

115. (New) The method of claim 74, wherein the vaccine or immunogenic composition further comprises an aluminum salt adjuvant.

116. (New) The method of claim 115, wherein the vaccine or immunogenic composition comprises from about 100 μg to about 600 μg or from about 100 μg to about 450 μg or from about from about 100 μg to about 300 μg or from about 150 μg to about 250 μg or from about 100 μg to about 225 μg or about 200 μg of an aluminum salt as adjuvant.

117. (New) The method of claim 115, wherein the adjuvant is aluminum hydroxide.

118. (New) The method of claim 115, wherein at least 75%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or 100% of the antigen are adsorbed to the adjuvant.

119. (New) The method of claim 74, wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.

120. (New) The method of claim 74, wherein the vaccine or immunogenic composition comprises a dose of about 10 μg of purified inactivated whole virus, about 200 μg aluminum hydroxide, a buffer; and optionally a sugar such as sucrose.

121. (New) The method of claim 74, wherein administration of the vaccine or immunogenic composition to the pregnant human subject does not result in the pregnant human subject having a severe adverse event as a result of the administration.

122. (New) The method of claim 121, wherein the severe adverse event is a fever of a temperature of 39°C or higher.

123. (New) The method of claim 74, wherein the pregnant human subject is from a Zika endemic region or from a Zika non-endemic region travelling to an endemic region.

124. (New) The method of claim 74, wherein the pregnant human subject is 18 to 29 years of age or 30 to 49 years of age.

REMARKS

Status of Claims

Claim 65-124 are pending. Claims 1-64 are canceled. Claims 55-64 drawn to the non-elected invention are canceled in the present response. Claims 65, 66, and 71-73, are currently amended. Claims 74-124 are new. Amendments to the claims and the new claims are supported in the specification as originally filed, and no new matter is introduced. For example, the amendments and new claims 74-124 are supported in the Applicant's PCT Application (WO 2019/090238) at paragraphs [00273, 00300, 00293, 0034, 00241, 00172, 0058, 0065, 00171] and original PCT claims 17, 37, 39, 47, 3-7, 10-14, 20, and 30-33.

Excess claim fees

Please charge the requisite fee of $4,000.00 for forty excess claims to Deposit Account No. 503145, referencing Attorney Docket No. 271634-488062.

Election/Restrictions under 35 U.S.C. 121 & 372

In the Restriction Requirement dated January 28, 2022, the Examiner has required that Applicant elect a single invention to which the claims must be restricted from the one of the following groups:

I. Claims 55-64; drawn to a vaccine or immunogenic composition comprising a dose of 1 μg to 40 μg of one antigen from a Zika virus, wherein the antigen is an activated whole virus.

II. Claims 65-73, drawn to a method of treating or preventing, in particular preventing Zika virus infection in a subject in need thereof, comprising administering to the subject the vaccine or immunogenic composition of claim 55.

Without acquiescing to the propriety of the present Restriction Requirement, and solely for advancing prosecution, the Applicant elects **Group II, without traverse**. Claims 65-124 read on the elected invention.

CONCLUSION

Applicant believes this reply is fully responsive to the Restriction Requirement dated February 28, 2022. Applicant reserves the right to file divisional applications or take such other appropriate action as deemed necessary to protect the subject matter restricted, canceled, or withdrawn from this application.

Applicant hereby petitions the Office for a two month extension of time under 37 CFR 1.136(a) and provides the fee set forth in 37 CFR §1.17(a)(2). Accordingly, the Applicant hereby authorizes the Patent Office to charge Deposit Account Number 50-3145 the $640.00 fee in accordance with 37 CFR § 1.17(a)(2) to cover the two month extension of time. However, should there be any deficiencies in payment, or charges required to maintain this application in good order, please deduct those charges from Deposit Account No. 50-3145, referencing Attorney Docket No. 271634-488062, and notify the undersigned attorney directly immediately.

Respectfully submitted,

Dated: June 28, 2022

/ Fernando Alberdi /

Fernando Alberdi, Ph.D.
Reg. No.: 62,688
HONIGMAN LLP
650 Trade Centre Way, Suite 200
Kalamazoo, Michigan 49002-0402
Telephone: (734) 418-4264
Facsimile: (734) 418- 4265
Email: falberdi@honigman.com;
Patents@honigman.com

PTO/SB/08a (02-18)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	16761329
	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	1648
	Examiner Name	Barry A. CHESTNUT
	Attorney Docket Number	271634-488062

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	1	20130280295	A1	2013-10-24	Intercell AG	
	2	20070110759	A1	2007-05-17	Sattentau et al.	
	3	20170014502	A1	2017-01-19	SUMATHY et al.	
	4	20200360505	A1	2020-11-19	LIVENGOOD et al.	
	5	20210177959	A1	2021-06-17	LIVENGOOD et al.	

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	Attorney Docket Number	271634-488062

	6	20210106669	A1	2021-04-15	LIVENGOOD et al.	
	7	20210403879	A1	2021-12-30	LIVENGOOD et al.	

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	1	EP 1 724 338 A1	EP	A1	2006-11-22	Crucell Holland B.V.		
	2	CN 107537029 A	CN	A	2018-01-05	SINOVAC BIOTECH CO LTD		☒
	3	CN 105749268 A	CN	A	2016-07-13	SINOVAC RES & DEV CO LTD		☒
	4	WO 2013/083726 A1	WO	A1	2013-06-13	Intercell AG		☐
	5	WO 2016/145149 A1	WO	A1	2016-09-15	THE UNITED STATES OF AMERICA, et al;		☐
	6	WO 2017/109223 A1	WO	A1	2017-06-29	VALNEVA SE		☐
	7	WO 2017/109224 A1	WO	A1	2017-06-29	VALNEVA SE		☐

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	Examiner Name	Barry A. CHESTNUT
	Attorney Docket Number	271634-488062

	8	WO 2017/109227 A1	WO	A1	2017-06-29	VALNEVA AUSTRIA GMBH		☐
	9	WO 2017/109228 A1	WO	A1	2017-06-29	VALNEVA AUSTRIA GMBH		☐
	10	WO 2007/007344 A1	WO	A1	2007-01-18	PANACEA BIOTEC LTD.		☐
	11	WO 2016/063291 A1	WO	A1	2016-04-28	SERUM INSTITUTE OF INDIA PRIVATE LIMITED		☐
	12	WO 2017/009873 A1	WO	A1	2017-01-19	BHARAT BIOTECH INTERNATIONAL LIMITED		☐
	13	WO 2017/109225 A1	WO	A1	2017-06-29	VALNEVA AUSTRIA GMBH		☐
	14	WO 2017/210215 A1	WO	A1	2017-12-07	THE GOVERMENT OF THE UNITED STATES, et al.		☐
	15	WO 2020/226831 A1	WO	A1	2020-11-12	TAKEDA VACCINES, INC.		☐
	16	WO 99/11762	WO	A1	1999-03-11	CHEIL JEDANG CORPORATION, et al.		☐
	17	WO 2008/026225 A2	WO	A2	2008-03-06	BHARAT BIOTECH INTERNATIONAL LIMITED		☐
	18	WO 2012/172574 A1	WO	A1	2012-12-20	BHARAT BIOTECH INTERNATIONAL LIMITED		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	1648
	Examiner Name	Barry A. CHESTNUT
	Attorney Docket Number	271634-488062

	19	WO 2015/059714 A1	WO	A1	2015-04-30	BHARAT BIOTECH INTERNATIONAL LIMITED		☐
	20	108187036	CN	A	2018-06-22	Sinovac Res & Dev Co Ltd		☒
	21	0864646	EP	A2	1998-09-16	Immuno AG		☒
	22	2017/192856	WO	A1	2017-11-09	Univ Miami		☐
	23	2019/090233	WO	A2	2019-05-09	Takeda Vaccines, Inc		☐
	24	2019/090228	WO	A2	2019-05-09	Takeda Vaccines, Inc		☐
	25	2019/108970	WO	A1	2019-06-06	Takeda Vaccines, Inc		☐
	26	2019/108976	WO	A1	2019-06-06	Takeda Vaccines, Inc		☐

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	1	MARTINEZ, L. J., et al; "Safety and Immunogenicity of a Dengue Virus Serotype-1 Purified-Inactivated Vaccine: Results of a Phase 1 Clinical Trial"; Am. J. Trop. Med. Hyg.; Vol. 93(3); 2015; p. 454–460, Copyright © 2015 by The American Society of Tropical Medicine and Hygiene;	

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	Art Unit	1648
	Examiner Name	Barry A. CHESTNUT
	Attorney Docket Number	271634-488062

	2	MAVES, R. C., et al; "Immunogenicity and protective efficacy of a psoralen-inactivated dengue-1 virus vaccine candidate in Aotus nancymaae monkeys"; Vaccine Vol. 29; (2011); p. 2691–2696;	
	3	MONATH, T. P., et al; "Inactivated yellow fever 17D vaccine: Development and nonclinical safety, immunogenicity and protective activity"; Vaccine Vol. 28; (2010); p. 3827–3840;	
	4	PEREIRA, R. C., et al; "An inactivated yellow fever 17DD vaccine cultivated in Vero cell cultures"; Vaccine Vol. 33; (2015); p. 4261–4268;	
	5	PETERSEN, L. R., et al; "Zika Virus"; The new england journal of medicine; March 30, 2016; 374:1552-63; DOI: 10.1056/NEJMra1602113; Massachusetts Medical Society.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16761329
	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	1648
	Examiner Name	Barry A. CHESTNUT
	Attorney Docket Number	271634-488062

	45	NCT03008122 "Phase I, Randomized, Double-blinded, Placebo-Controlled Dose De-escalation Study to Evaluate Safety and Immunogenicity of Alum Adjuvanted Zika Virus Purified Inactivated Vaccine (ZPIV) in Adults in a Flavivirus Endemic Area", Clinical Trials.gov, 2 January 2017, Retrieved from internet 30 April 2022, 10 pages	
	46	PRESS RELEASE; "Walter Reed Scientists Test Zika Vaccine Candidate"; DOD News; 9 June 2016;	
	47	Database GenBank Accession No.KY583506.1; "Synthetic construct polyprotein gene, complete cds", Retrieved from GenBank Accession No. KY583506.1; 6 February 2018, https://www.ncbi.nlm.nih.gov/nuccore/KY583506.1, 5 pages	
	48	SHAWAN, M. M. A. K., et al; "In Silico Modeling and Immunoinformatics Probing Disclose the Epitope Based Peptide Vaccine Against Zika Virus Envelope Glycoprotein"; Indian Journal of Pharmaceutical and Biological Research (IJPBR); Vol. 2(4); p. 44-57; 2014;	
	49	Database GenBank Accession No. KX087101.3; "Zika virus strain ZIKV/Homo sapiens/PRI/PRVABC59/2015, complete genome", Retrieved from GenBank Accession No. KX087101.3; 18 November 2016, https://www.ncbi.nlm.nih.gov/nuccore/KX087101, 4 pages	
	50	WORLD HEALTH ORGANIZATION; "Current Zika Product Pipeline"; Product Information; 3 March 2016;	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16761329
	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	1648
	Examiner Name	Barry A. CHESTNUT
	Attorney Docket Number	271634-488062

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Fernando Alberdi/	Date (YYYY-MM-DD)	2022-06-28
Name/Print	Fernando Alberdi, Ph.D.	Registration Number	62,688

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/761,329	05/04/2020	Jill A LIVENGOOD	271634-488062	5672

114119 7590 02/28/2022

Honigman LLP/ MPI
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER	
CHESTNUT, BARRY A	

ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
02/28/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketing@takeda.com
patents@honigman.com

Office Action Summary	Application No. 16/761,329	Applicant(s) LIVENGOOD et al.	
	Examiner Barry Chestnut	Art Unit 1648	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 05/04/2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 55-73 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☑ Claim(s) 55-73 are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

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 accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group 1, claims 55-64, drawn to a vaccine or immunogenic composition comprising a dose of 1ug to 40ug of one antigen from a Zika virus, wherein the antigen is an inactivated whole virus.

Group 2, claims 65-73, drawn to a method of treating or preventing, in particular preventing Zika virus infection in a subject in need thereof, comprising administering to the subject the vaccine or immunogenic composition of claim 55.

The groups 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 cited reasons:

Barbero *et al.* (WO2017109223) discloses a Zika virus vaccine, purified by sucrose gradient centrifugation, and inactivated with formalin, at antigen doses of 0.012-12 ug, and adjuvanted with $AlOH_3$. In light of Barbero *et al.*, the composition of the present invention is disclosed in the teachings of the art; therefore, there is no special technical feature uniting the claimed inventions.

REQUIREMENT FOR UNITY OF INVENTION

As provided in 37 CFR 1.475(a), a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in a national stage application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. See 37 CFR 1.475(e).

WHEN CLAIMS ARE DIRECTED TO MULTIPLE CATEGORIES OF INVENTIONS

As provided in 37 CFR 1.475(b), a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(a) An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

(b) An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or

(2) A product and process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

(c) If an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b) of this section, unity of invention might not be present.
(d) If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and § 1.476(c).
(e) The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**. The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention. Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. Failure to do so may result in no rejoinder. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Barry Chestnut whose telephone number is (571)270-3546. The examiner can normally be reached on M-F 8am-4pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BARRY A CHESTNUT/
Primary Examiner, Art Unit 1648

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/761,329	05/04/2020		2520	38011U	19	1

CONFIRMATION NO. 5672

FILING RECEIPT

20529
NATH, GOLDBERG & MEYER
Joshua Goldberg
112 South West Street
Alexandria, VA 22314

OC000000123962229

Date Mailed: 03/11/2021

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Jill A LIVENGOOD, Cambridge, MA;
Hansi DEAN, Cambridge, MA;
Htay Htay HAN, Cambridge, MA;
Raman RAO, Singapore, SINGAPORE;
Jackie MARKS, Cambridge, MOROCCO;
Gary DUBIN, Glattpark-Opfikon, Zurich, SWITZERLAND;
Laurence DE MOERLOOZE, Glattpark-Opfikon, Zurich, SWITZERLAND;
Hetal PATEL, Cambridge, MA;
Sushma KOMMAREDDY, Cambridge, MA;

Applicant(s)

TAKEDA VACCINES, INC., Cambridge, MA;

Power of Attorney: The patent practitioners associated with Customer Number 20529

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US2018/059233 11/05/2018
which claims benefit of 62/581,500 11/03/2017
and claims benefit of 62/592,995 11/30/2017 *
(*)Data provided by applicant is not consistent with PTO records.

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 03/09/2021

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/761,329**

Projected Publication Date: 06/17/2021

Non-Publication Request: No

Early Publication Request: No
Title

ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign

patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	16/761,329
Filing Date	May 4, 2020
First Named Inventor	Jill A. LIVENGOOD
Title	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	38011U

SIGNATURE of Applicant or Patent Practitioner

Signature	/Joshua B. Goldberg/	Date (Optional)	
Name	Joshua B. Goldberg	Registration Number	44126
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Doc Code: PA..
Document Description: Power of Attorney

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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 20529

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

TAKEDA VACCINES, INC.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	October 11, 2018
Name	Dr. Oliver Mechnich		
Title	Senior Director IP		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS AND METHODS OF USING THE SAME

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number PCT/US2018/059233

filed on 05 November 2018

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: JILL A. LIVENGOOD Date (Optional): 04 July 2019

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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Privacy Act Statement

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS AND METHODS OF USING THE SAME

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☒ United States application or PCT international application number PCT/US2018/059233 filed on 05 November 2018.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Hansi DEAN Date (Optional): 01 Jun 2020

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

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☒ United States application or PCT international application number PCT/US2018/059233

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LEGAL NAME OF INVENTOR

Inventor: Htay Htay HAN Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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☐ The attached application, or

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LEGAL NAME OF INVENTOR

Inventor: Raman RAO Date (Optional): 04/09/2018

Signature:

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS AND METHODS OF USING THE SAME

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☒ United States application or PCT international application number PCT/US2018/059233 filed on 05 November 2018

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Jackie MARKS Date (Optional): _____

Signature: _____

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LEGAL NAME OF INVENTOR

Inventor: Gary DUBIN Date (Optional): 7 July 2020

Signature: _____

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LEGAL NAME OF INVENTOR

Inventor: Laurence DE MOERLOOZE Date (Optional): _____

Signature: _____

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LEGAL NAME OF INVENTOR

Inventor: Hetal PATEL Date (Optional): 27 JULY 2020

Signature: HPatel

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8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS AND METHODS OF USING THE SAME

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number PCT/US2018/059233 filed on 05 November 2018

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available

LEGAL NAME OF INVENTOR

Inventor: Sushma KOMMAREDDY Date (Optional): 30 June 2020

Signature: Sushma K

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	41923024
Application Number:	16761329
International Application Number:	
Confirmation Number:	5672
Title of Invention:	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME
First Named Inventor/Applicant Name:	Jill A LIVENGOOD
Customer Number:	20529
Filer:	Stanley Protigal/Amanda Suazo
Filer Authorized By:	Stanley Protigal
Attorney Docket Number:	38011U
Receipt Date:	15-FEB-2021
Filing Date:	
Time Stamp:	16:30:18
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	SubmissiontoCompleteFilingReqs.pdf	21800 2c975e35cbb1177f4d36a5e1d8f90c3854157150	no	1

Warnings:

Information:					
2	Power of Attorney	POA.pdf	503488 610466a93b69031cfd08d1d606cfdd6ff18eed08	no	2
Warnings:					
Information:					
3	Oath or Declaration filed	DECS.pdf	10321210 1723c295679ae0fa9f6096e2b0c9dd520cd14e5e	no	18
Warnings:					
Information:					
			Total Files Size (in bytes):	10846498	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Mail Stop PCT
Attorney Docket: 38011U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

	LIVENGOOD, et al.	Conf. No.:	5672
Appl. No.:	16/761,329	Examiner:	TBD
Filed:	May 4, 2020	Art Unit:	TBD
Intl. Appl. No.:	PCT/US2018/059233		
Intl. Filing Date:	November 5, 2018		
Title:	**ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME**		

SUBMISSION OF DOCUMENTS TO COMPLETE FILING REQUIREMENTS UNDER 35 USC 371

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In order to complete the filing requirement under 35 USC 371 for the captioned application, applicant now submit the following documents:

(1) Nine (9) executed Declarations, 18 pages;
(2) One (1) Power of Attorney with transmittal, Form AIA82A-B, two (2) pages.

It is submitted that these documents are in compliance by being duly executed by the Inventors. The surcharge fee for the late filing of the executed inventor's declaration was paid with the application filed on May 4, 2020 and no further fees should be due.

The Examiner is welcome to telephone the undersigned attorney if he has any questions or comments.

Respectfully submitted,

NATH, GOLDBERG & MEYER

Date: February 15, 2021

/Joshua B. Goldberg/

Joshua B. Goldberg, Reg. No. 44,126
Customer No. 20529

NATH, GOLDBERG & MEYER
112 S. West Street, Alexandria, VA 22314
TEL: (703) 548-6284; FAX: (703) 683-8396
JBG/als

PCT REQUEST

(Original in Electronic Form)

0	**For receiving Office use only**	
0-1	International Application No.	PCT/US18/59233
0-2	International Filing Date	05 November 2018 (05.11.2018)
0-3	Name of receiving Office and "PCT International Application"	RO/US

0-4	**Form PCT/RO/101 PCT Request**	
0-4-1	Prepared Using	**ePCT-Filing for data package download Version 4.3.015 MT/FOP 20181031/1.1**
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	**United States Patent and Trademark Office (USPTO) (RO/US)**
0-7	**Applicant's or agent's file reference**	**741065**
I	**Title of Invention**	**ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME**
II	**Applicant**	
II-1	This person is	**Applicant only**
II-2	Applicant for	**All designated States**
II-4	Name	**TAKEDA VACCINES, INC.**
II-5	Address	**75 Sidney Street Cambridge, Massachusetts 02139 United States of America**
II-6	State of nationality	**US**
II-7	State of residence	**US**
II-10	e-mail	**docketingpatent@leydig.com**
II-10(a)	E-mail authorization The receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority are authorized to use this e-mail address, if the Office or Authority so wishes, to send notifications issued in respect of this international application:	**exclusively in electronic form (no paper notifications will be sent)**

PCT REQUEST

(Original in Electronic Form)

III-1	**Applicant and/or inventor**	
III-1-1	This person is	**Applicant only**
III-1-2	Applicant for	**All designated States**
III-1-4	Name	**THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES**
III-1-5	Address	**Office of Technology Transfer, National Institutes of Health 5601 Fishers Lane, Rm. 2G36, MSC 9804 Rockville, Maryland 20892 United States of America**
III-1-6	State of nationality	**US**
III-1-7	State of residence	**US**
III-1-10	e-mail	**docketingpatent@leydig.com**
III-1-10(a)	E-mail authorization The receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority are authorized to use this e-mail address, if the Office or Authority so wishes, to send notifications issued in respect of this international application:	**exclusively in electronic form (no paper notifications will be sent)**
III-2	**Applicant and/or inventor**	
III-2-1	This person is	**Inventor only**
III-2-3	Inventor for	**All designated States**
III-2-4	Name (LAST, First)	**LIVENGOOD, Jill A.**
III-2-5	Address	**c/o Takeda Vaccines, Inc. 75 Sidney Street Cambridge, Massachusetts 02139 United States of America**
III-3	**Applicant and/or inventor**	
III-3-1	This person is	**Inventor only**
III-3-3	Inventor for	**All designated States**
III-3-4	Name (LAST, First)	**GIEBLER, Holli**
III-3-5	Address	**c/o Takeda Vaccines, Inc. 75 Sidney Street Cambridge, Massachusetts 02139 United States of America**
III-4	**Applicant and/or inventor**	
III-4-1	This person is	**Inventor only**
III-4-3	Inventor for	**All designated States**
III-4-4	Name (LAST, First)	**BALDWIN, Whitney**
III-4-5	Address	**c/o Takeda Vaccines, Inc. 75 Sidney Street Cambridge, Massachusetts 02139 United States of America**

PCT REQUEST

(Original in Electronic Form)

III-5	**Applicant and/or inventor**	
III-5-1	This person is	**Inventor only**
III-5-3	Inventor for	**All designated States**
III-5-4	Name (LAST, First)	**DEAN, Hansi**
III-5-5	Address	**Vaccine Business Unit Takeda Pharmaceuticals 40 Landsdowne Street Cambridge, Massachusetts 02139 United States of America**
IV-1	**Agent or common representative; or address for correspondence**	
	The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	**Agent**
IV-1-1	Name (LAST, First)	**SCHUBERT, Michael J.**
IV-1-2	Address	**Leydig, Voit & Mayer, Ltd. Two Prudential Plaza — Suite 4900 180 North Stetson Avenue Chicago, Illinois 60601-6731 United States of America**
IV-1-3	Telephone No.	**312-616-5600**
IV-1-4	Facsimile No.	**312-616-5700**
IV-1-5	e-mail	**docketingpatent@leydig.com**
IV-1-5(a)	E-mail authorization The receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority are authorized to use this e-mail address, if the Office or Authority so wishes, to send notifications issued in respect of this international application:	**exclusively in electronic form (no paper notifications will be sent)**
IV-1-6	Agent's registration No.	**72,107**
V	**DESIGNATIONS**	
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**	
VI-1	**Priority claim of earlier national application**	
VI-1-1	Filing date	**03 November 2017 (03.11.2017)**
VI-1-2	Number	**62/581,500**
VI-1-3	Country or Member of WTO	**US**

PCT REQUEST

(Original in Electronic Form)

VI-2	**Priority claim of earlier national application**		
VI-2-1	Filing date	**30 November 2017 (30.11.2017)**	
VI-2-2	Number	**62/592,995**	
VI-2-3	Country or Member of WTO	**US**	
VI-3	**Priority document request** The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	**VI-1** **VI-2**	
VI-4	**Incorporation by reference :** where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.		
VII-1	**International Searching Authority Chosen**	**European Patent Office (EPO) (ISA/EP)**	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

PCT REQUEST

(Original in Electronic Form)

IX	Check list	Number of sheets	Electronic file(s) attached
IX-1	Request (including declaration sheets)	**5**	✓
IX-2	Description	**135**	✓
IX-3	Claims	**7**	✓
IX-4	Abstract	**1**	✓
IX-5	Drawings	**29**	✓
IX-6a	Sequence listing part of the description (also to be used for the purposes of international search)	**-**	✓
IX-7	TOTAL	**177**	
	Accompanying Items	Paper document(s) attached	Electronic file(s) attached
IX-8	Fee calculation sheet	**-**	✓
IX-20	**Figure of the drawings which should accompany the abstract**	**1**	
IX-21	**Language of filing of the international application**	**English**	
X-1	**Signature of applicant, agent or common representative**	**/Michael J. Schubert, Reg. No. 72,107/**	
X-1-1	Name (LAST, First)	**SCHUBERT, Michael J.**	
X-1-3	Capacity (if such capacity is not obvious from reading the request)	**Agent**	

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	05 November 2018 (05.11.2018)
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	**ISA/EP**
10-6	**Transmittal of search copy delayed until search fee is paid**	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	
	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	38011U

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2017/009873	WO	A1	2017-01-19	BHARAT BIOTECH INTERNATIONAL LIMITED		
	2	2017/109223	WO	A1	2017-06-29	VALNEVA SE		

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	38011U

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	International Search Report dated March 15, 2019 issued in corresponding Application No. PCT/US2018/059233	
	2	TIWARI, et al., "Assessment of immunogenic potential of Vero adapted formalin inactivated vaccine derived from novel ECSA genotype of Chikungunya virus", Vaccine, Vol. 27, No. 18, pp. 2513-2522, 2009.	
	3	BALDWIN, et al., "Purified Inactivated Zika Vaccine Candidates Afford Protection against Lethal Challenge in Mice", Scientific Reports, Vol. 8, No. 1	
	4	SHAN, et al., "A live-attenuated Zika virus vaccine candidate induces sterilizing immunity in mouse models", Nature Medicine, Vol. 23, No. 6, pp. 763-767, 2017.	
	5	DRUELLE, et al., "Wild type measles virus attenuation independent of type I IFN", Virology Journal, Vol. 5, No. 1, 2008.	
	6	WEGER-LUCARELLI, et al., "Development and Characterization of Recombinant Virus Generated from a New World Zika Virus Infectious Clone", Journal of Virology, Vol. 91, No. 1, 2016.	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2020-05-04
	First Named Inventor	Jill A. LIVENGOOD
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	38011U

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Joshua B. Goldberg/	Date (YYYY-MM-DD)	2020-05-04
Name/Print	Joshua B. Goldberg	Registration Number	44126

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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The information provided by you in this form will be subject to the following routine uses:

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
09 May 2019 (09.05.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/090238 A1

(51) International Patent Classification:
A61K 39/12 (2006.01) *A61P 31/14* (2006.01)

(21) International Application Number:
PCT/US2018/059233

(22) International Filing Date:
05 November 2018 (05.11.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/581,500 03 November 2017 (03.11.2017) US
62/592,995 30 November 2017 (30.11.2017) US

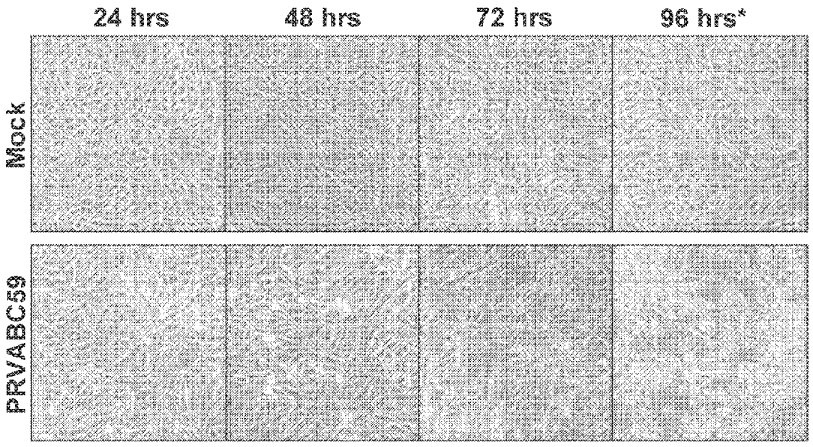
(71) Applicants: **TAKEDA VACCINES, INC.** [US/US]; 75 Sidney Street, Cambridge, Massachusetts 02139 (US). **THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; Office of Technology Transfer, National Institutes of Health, 5601 Fishers Lane, Rm. 2G36, MSC 9804, Rockville, Maryland 20892 (US).

(72) Inventors: **LIVENGOOD, Jill A.**; c/o Takeda Vaccines, Inc., 75 Sidney Street, Cambridge, Massachusetts 02139 (US). **DEAN, Hansi**; Vaccine Business Unit, Takeda Pharmaceuticals, 40 Landsdowne Street, Cambridge, Massachusetts 02139 (US). **HAN, Htay Htay**; c/o Takeda Vaccines, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US). **RAO, Raman**; c/o Takeda Vaccines Pte Ltd., 21 Biopolis Road; Nucleos North Tower, Level 4, 138567 Singapore (SG). **MARKS, Jackie**; c/o Takeda Vaccines, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US). **DUBIN, Gary**; c/o Takeda Pharmaceutical International AG, Thurgauerstrasse 130, 8152 Glattpark-Opfikon, Zurich (CH). **DE MOERLOOZE, Laurence**; c/o Takeda Pharmaceutical International AG, Thurgauerstrasse 130, 8152 Glattpark-Opfikon, Zurich (CH). **PATEL, Hetal**; c/o Takeda Vaccines, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US). **KOMMAREDDY, Sushma**; c/o Takeda Vaccines, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US).

(74) Agent: **SCHUBERT, Michael J.**; Leydig, Voit & Mayer, Ltd., Two Prudential Plaza — Suite 4900, 180 North Stetson Avenue, Chicago, Illinois 60601-6731 (US).

(54) Title: ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME

FIG. 1



(57) Abstract: The present disclosure relates to Zika virus vaccines and immunogenic compositions having one or more antigens from a Zika virus (*e.g.*, a Zika virus clonal isolate, a non-human cell adapted Zika virus, *etc.*), and methods of treatments and uses thereof.

[Continued on next page]

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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))*
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LEGAL NAME OF INVENTOR

Inventor: Hansi DEAN Date (Optional) :_____

Signature: _____

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Inventor: Gary DUBIN Date (Optional) :_____

Signature: _____

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LEGAL NAME OF INVENTOR

Inventor: Sushma KOMMAREDDY Date (Optional) :_____

Signature: _____

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

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As the below named inventor, I hereby declare that:

This declaration is directed to:

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☒ United States application or PCT international application number PCT/US2018/059233 filed on 05 November 2018.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Jill A. LIVENGOOD Date (Optional) :_____

Signature: _____

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LEGAL NAME OF INVENTOR

Inventor: Jacki MARKS Date (Optional) :_____

Signature: _____

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LEGAL NAME OF INVENTOR

Inventor: Laurence DE MOERLOOZE Date (Optional) :_____

Signature: _____

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4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS AND METHODS OF USING THE SAME

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number PCT/US2018/059233 filed on 05 November 2018.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Raman RAO Date (Optional) :_____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

FIG. 1

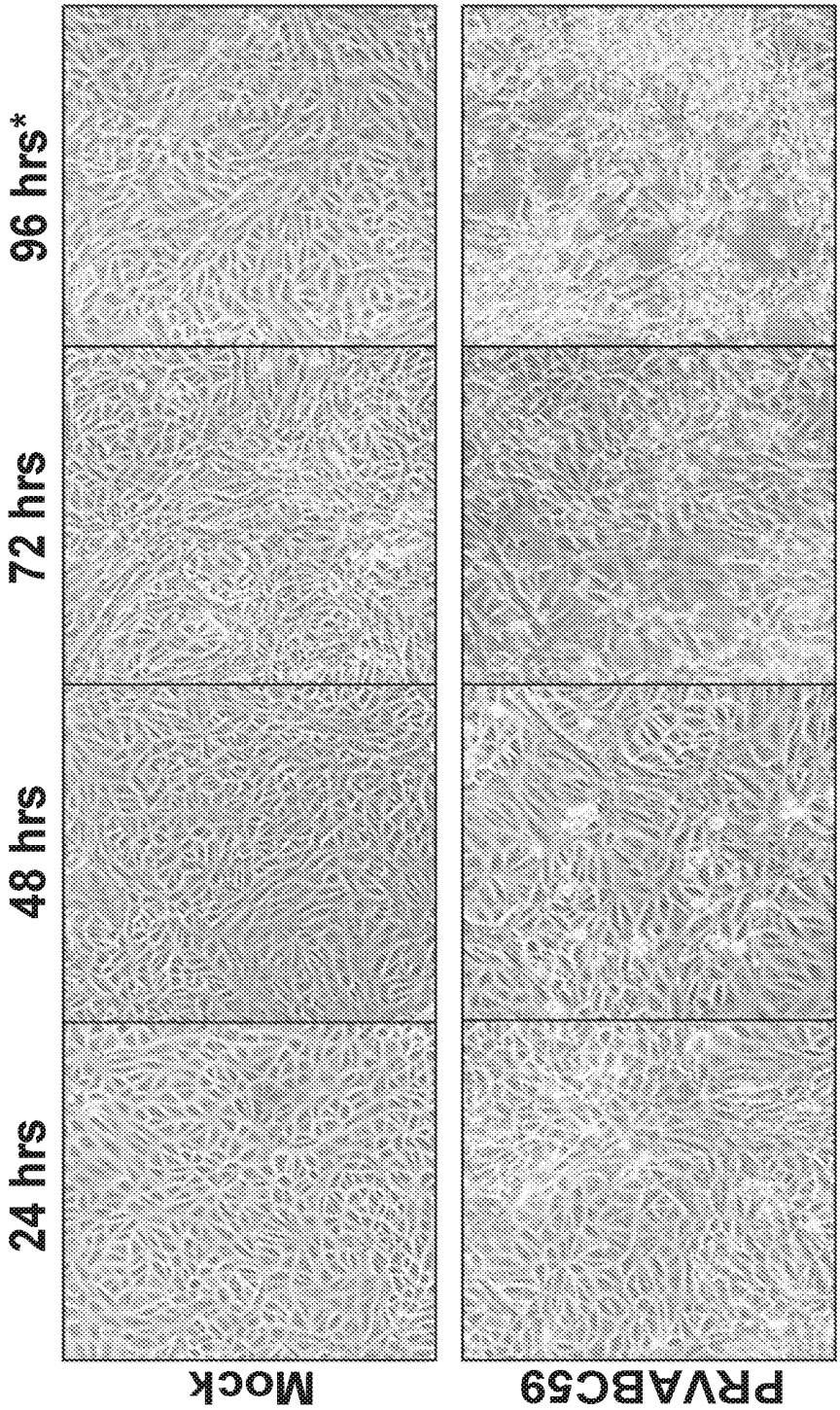


FIG. 2

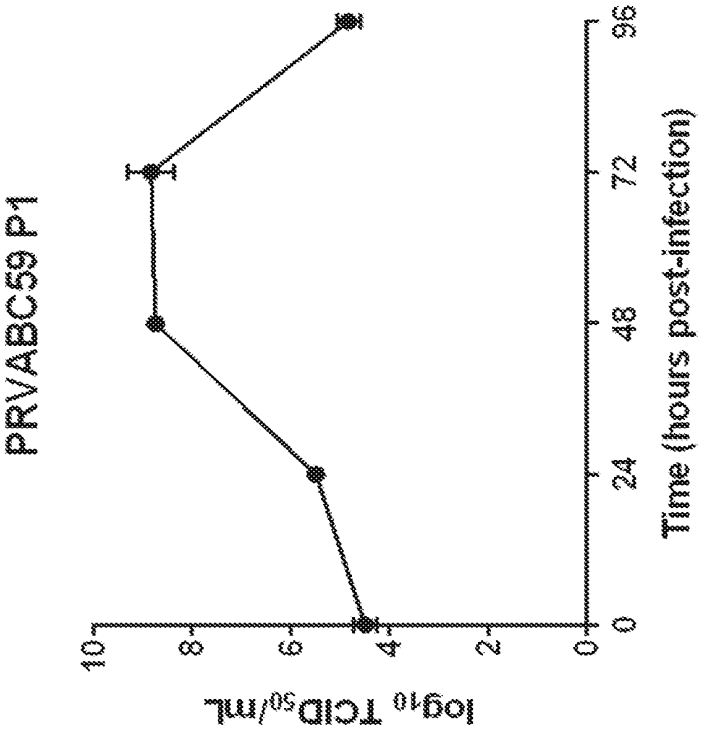

PRVABC59 P1
log10 TCID50/mL
10
8
6
4
2
0
0
24
48
72
96
Time (hours post-infection)

FIG. 3

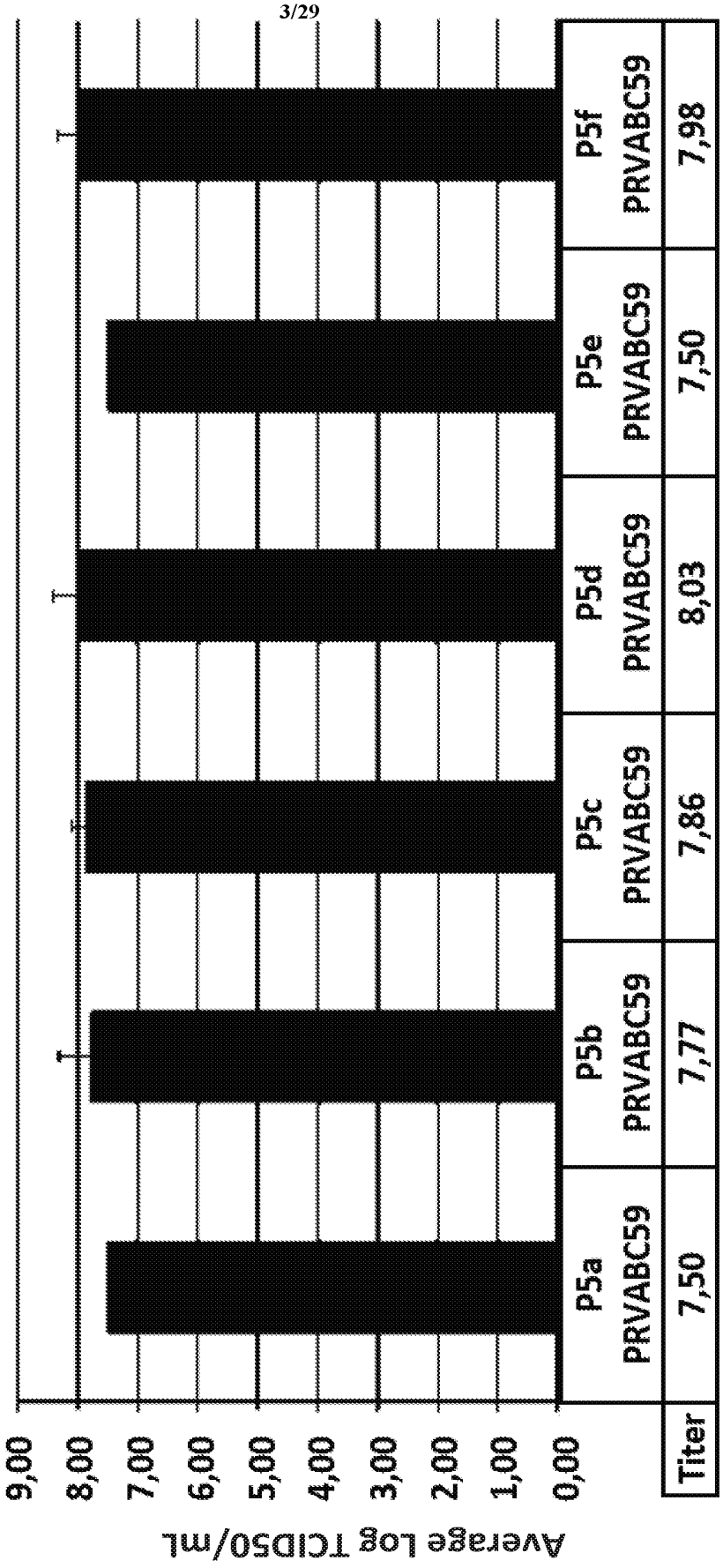

Average log TCID50/mL
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Titer
P5a PRVABC59
7,50
P5b PRVABC59
7,77
P5c PRVABC59
7,86
P5d PRVABC59
8,03
P5e PRVABC59
7,50
P5f PRVABC59
7,98

FIG. 4

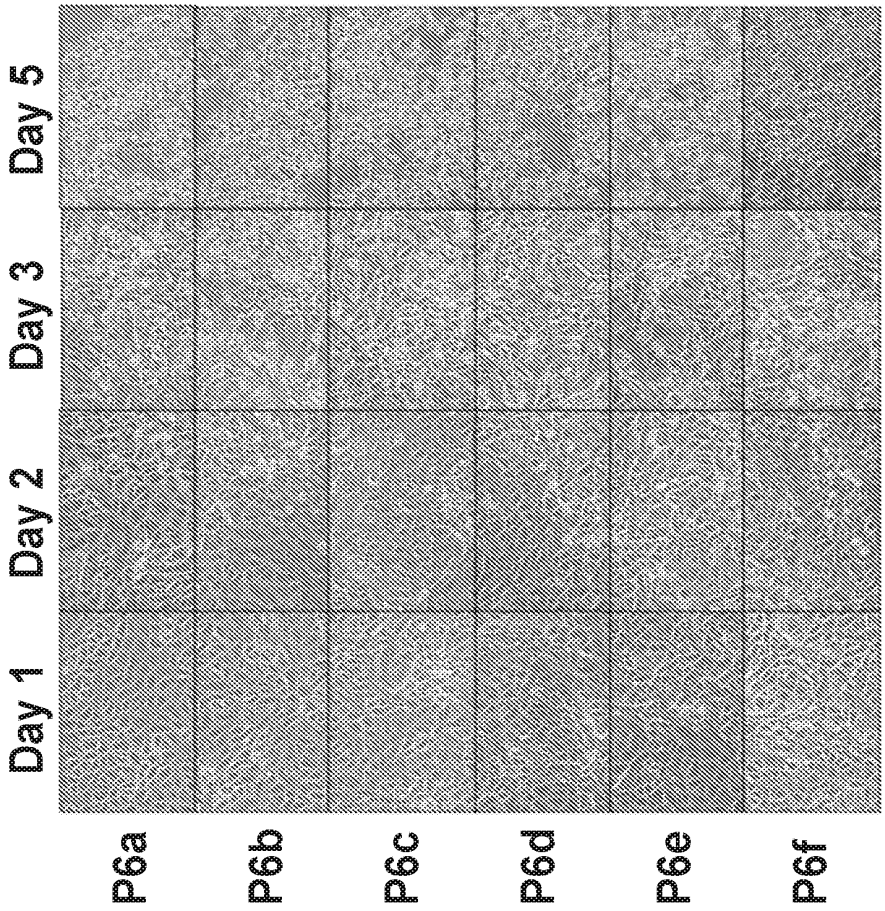

Harvest 1
Harvest 2
Day 1
Day 2
Day 3
Day 5
P6a
P6b
P6c
P6d
P6e
P6f

FIG. 5

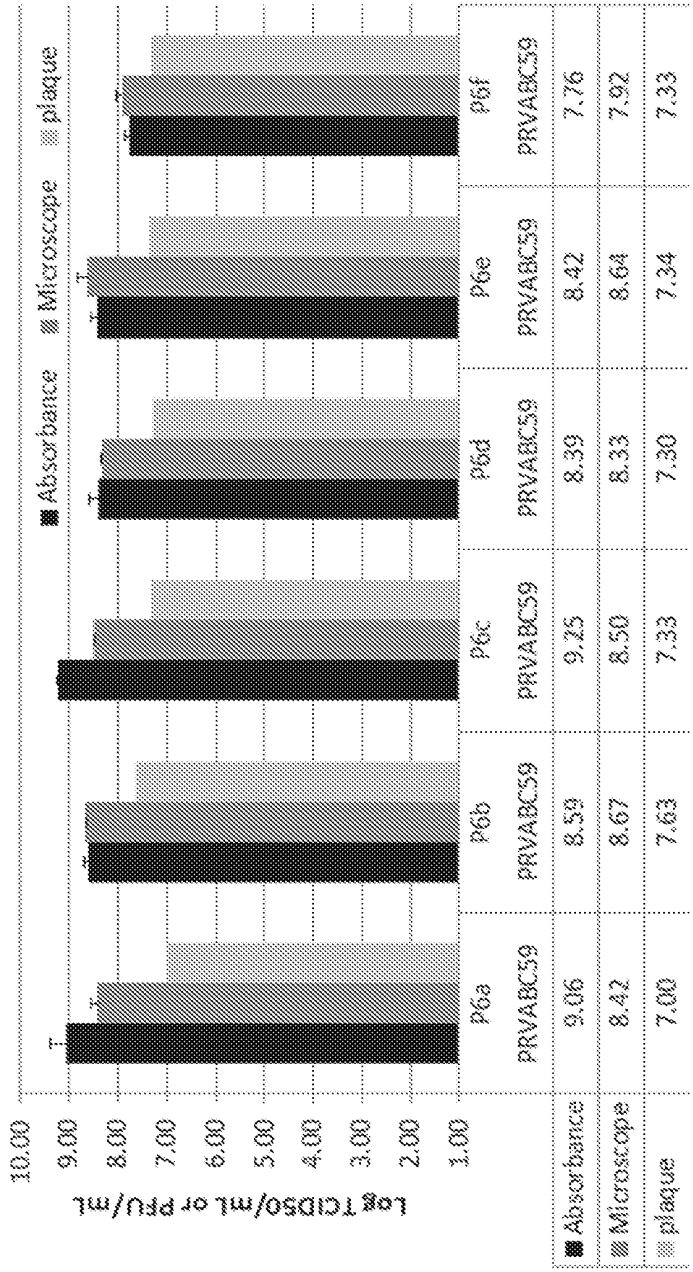

Absorbance
Microscope
plaque
Log TCID50/mL or PFU/mL
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
P6a
P6b
P6c
P6d
P6e
P6f
PRVABC59
Absorbance 9.06 8.59 9.25 8.39 8.42 7.76
Microscope 8.42 8.67 8.50 8.33 8.64 7.92
plaque 7.00 7.63 7.33 7.30 7.34 7.33

FIG. 6

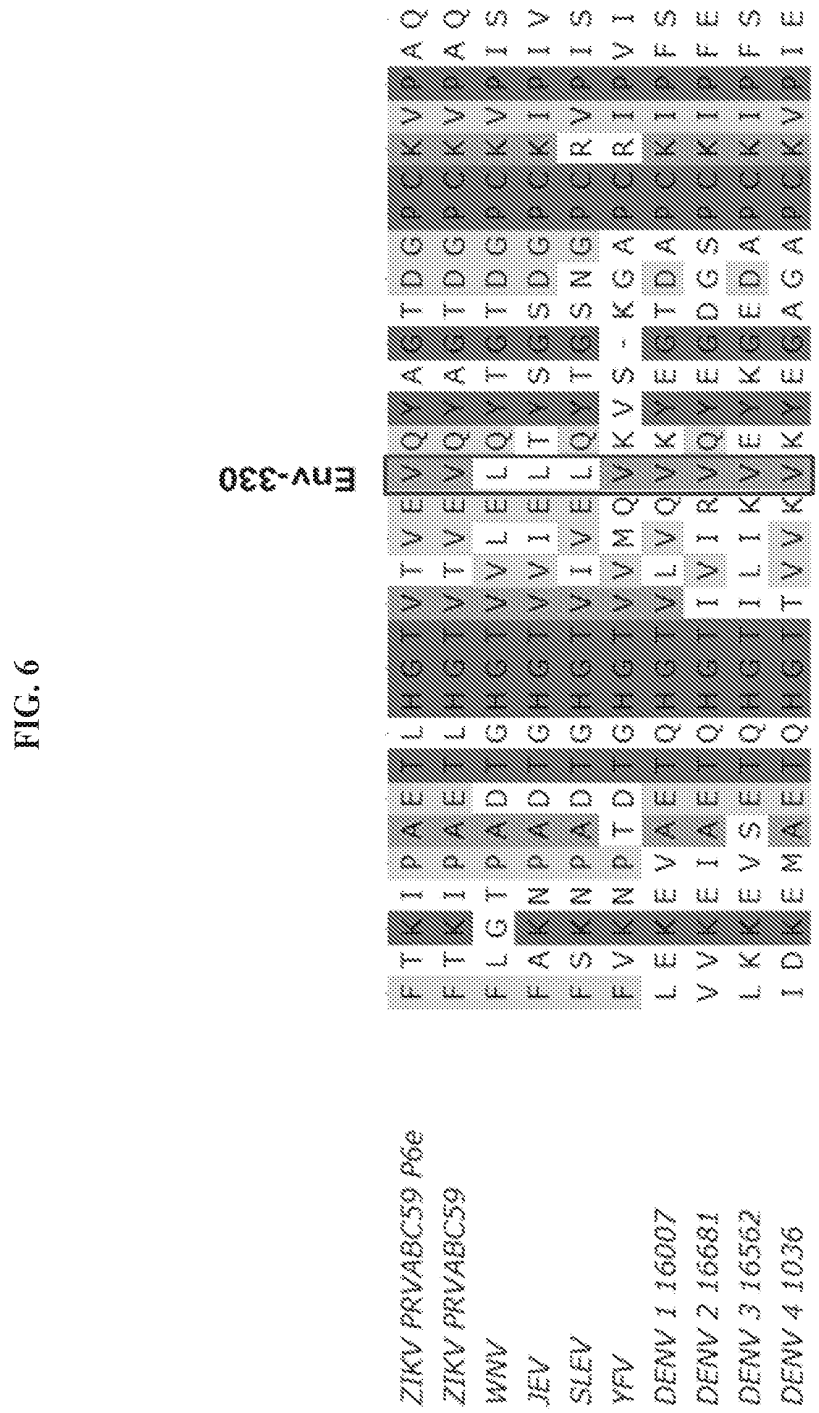

Env-330
ZIKV PRVABC59 P6e
ZIKV PRVABC59
WNV
JEV
SLEV
YFV
DENV 1 16007
DENV 2 16681
DENV 3 16562
DENV 4 1036

FIG. 7

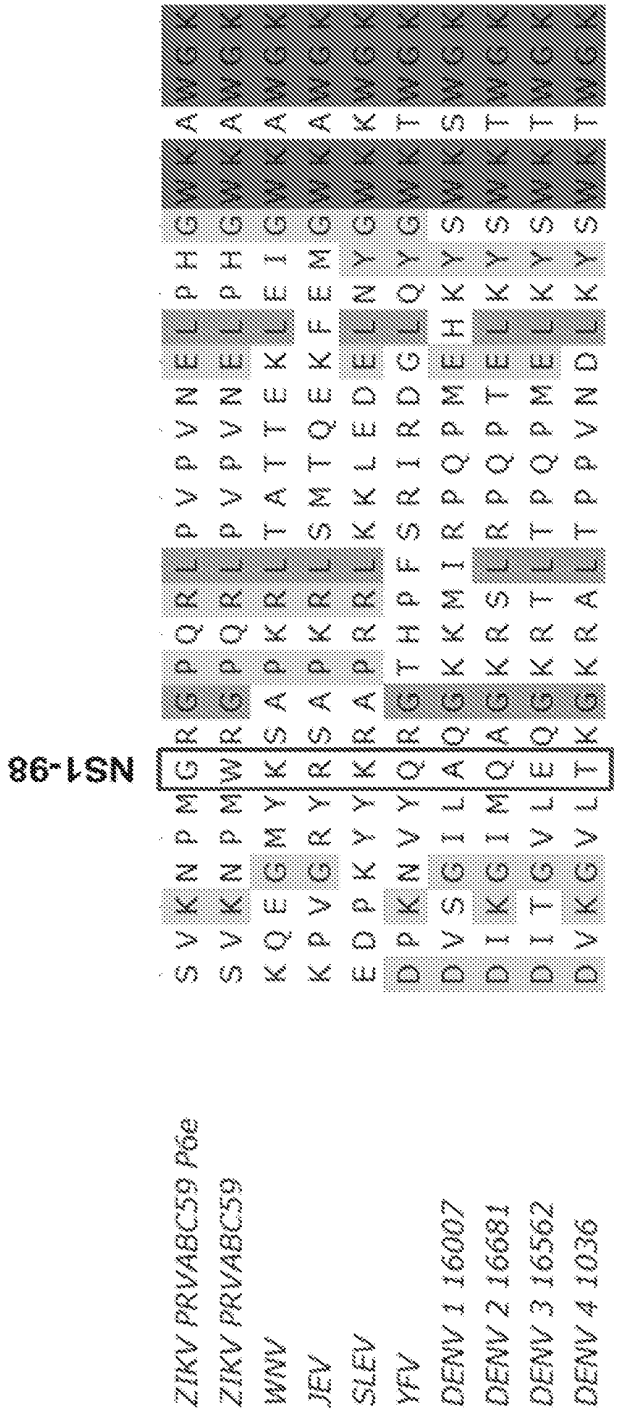

NS1-98
ZIKV PRVABC59 Poe
ZIKV PRVABC59
WNV
JEV
SLEV
YFV
DENV 1 16007
DENV 2 16681
DENV 3 16562
DENV 4 1036

FIG. 8

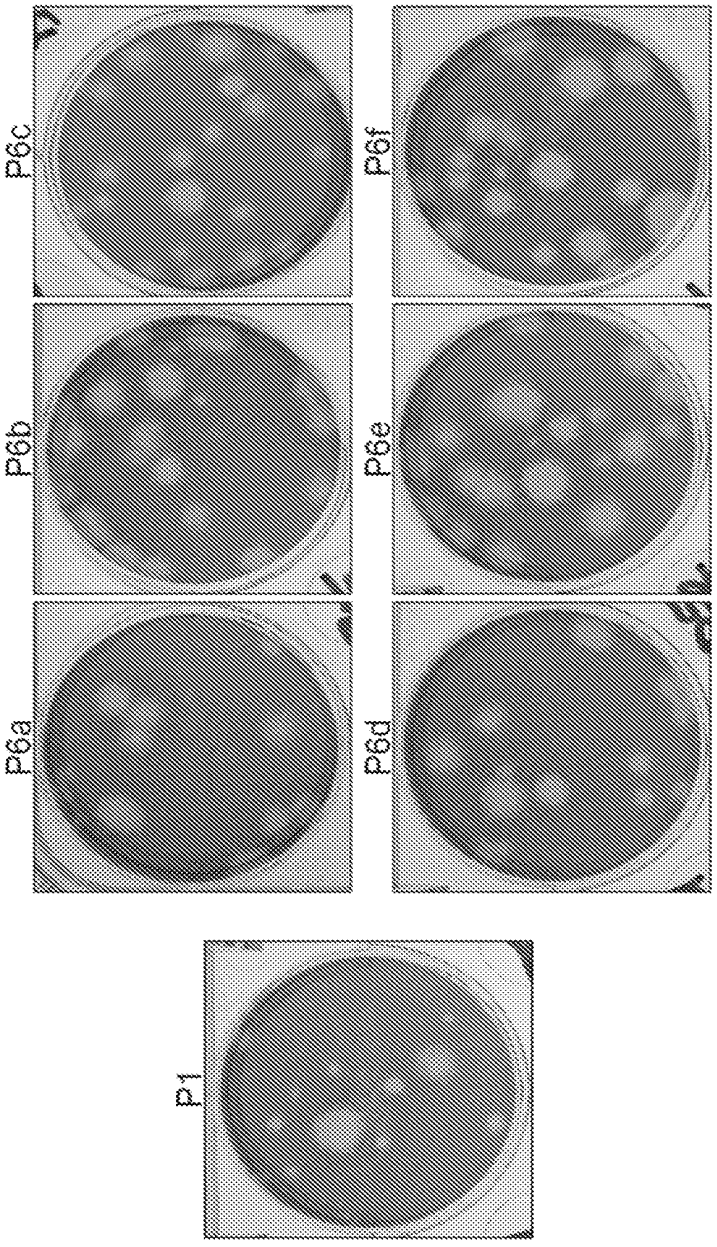


FIG. 9

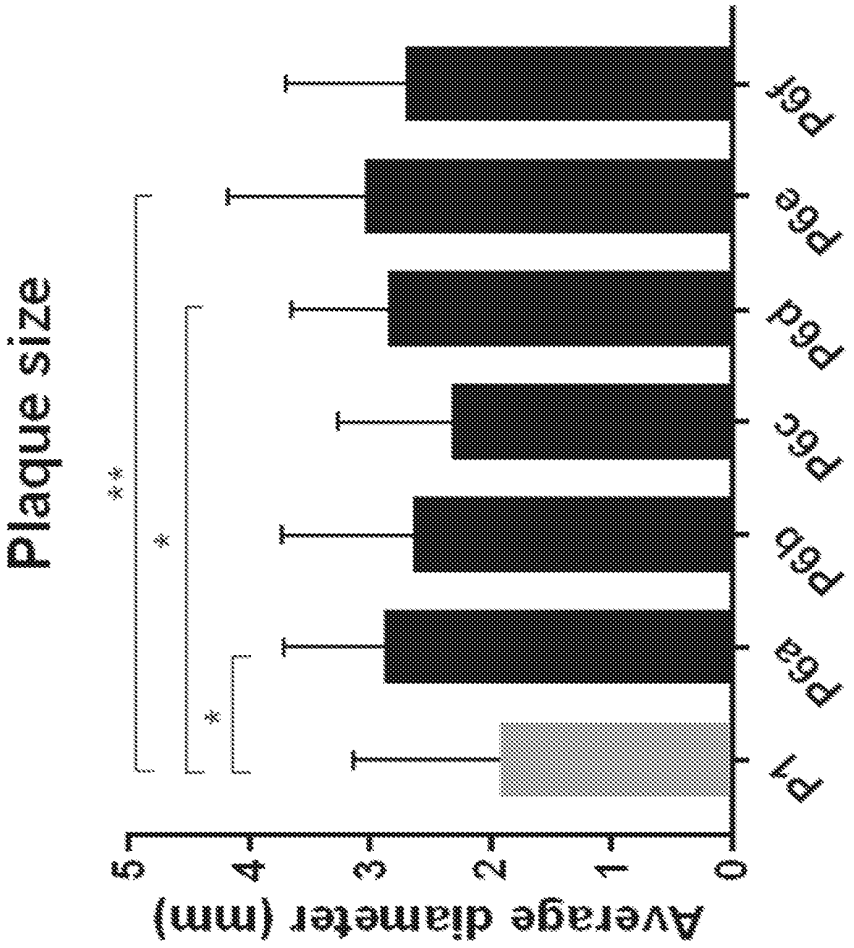

Plaque size
Average diameter (mm)
0
1
2
3
4
5
P1
P6a
P6b
P6c
P6d
P6e
P6f
*
*
**

FIG. 10

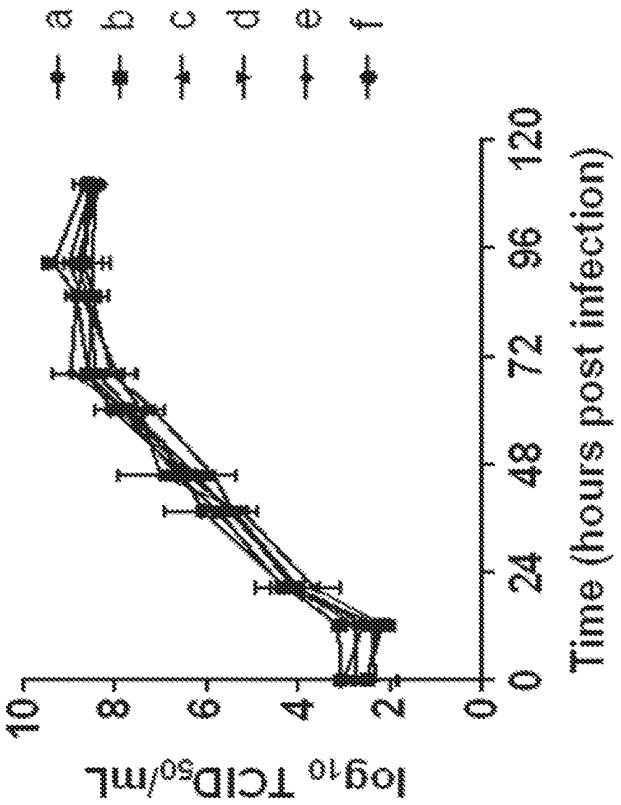

a
b
c
d
e
f
log10 TCID50/mL
10
8
6
4
2
0
0
24
48
72
96
120
Time (hours post infection)

FIG. 11

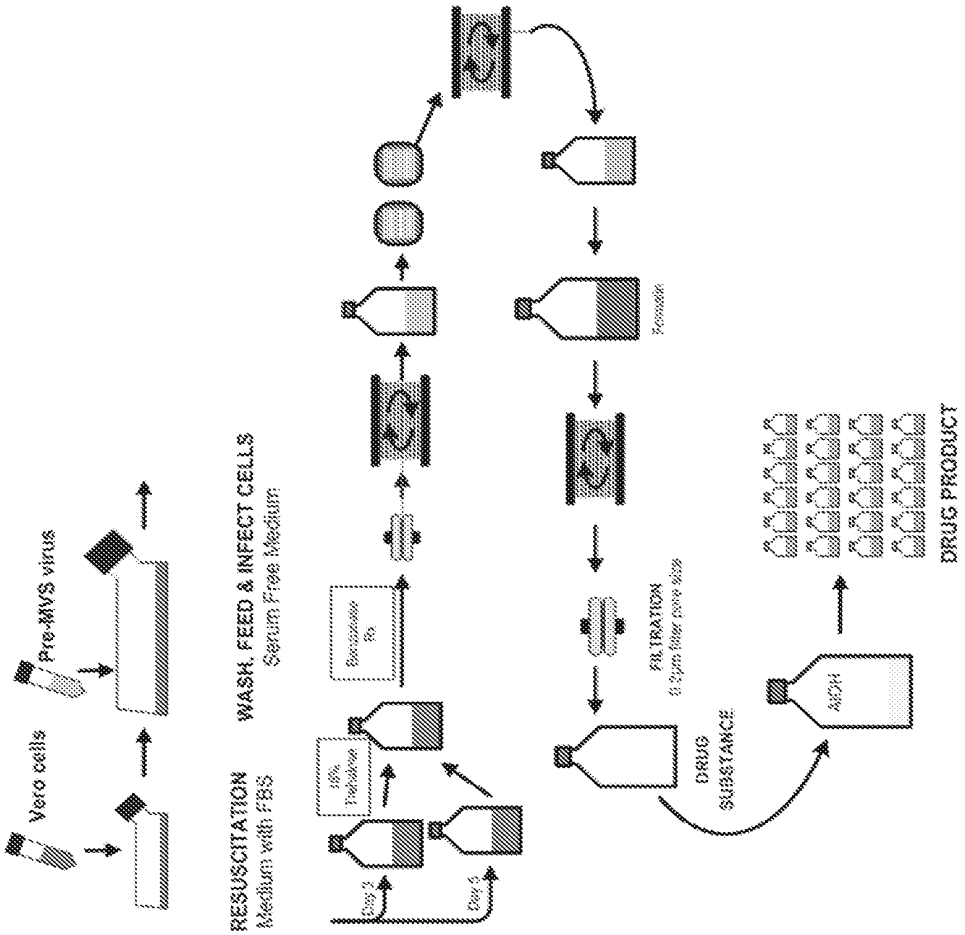

Vero cells
Pre-MVS virus
RESUSCITATION
Medium with FBS
WASH, FEED & INFECT CELLS
Serum Free Medium
Bioreactor
Day 3
Day 7
Benzonase
FILTRATION
DRUG
SUBSTANCE
AEX
DRUG PRODUCT

FIG. 12A

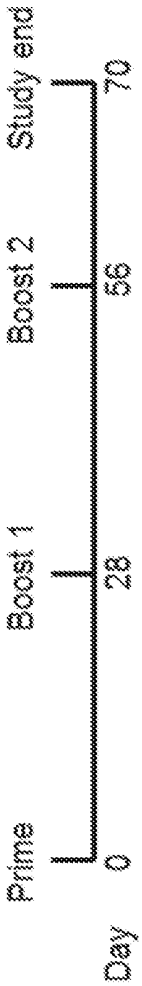


FIG. 12B

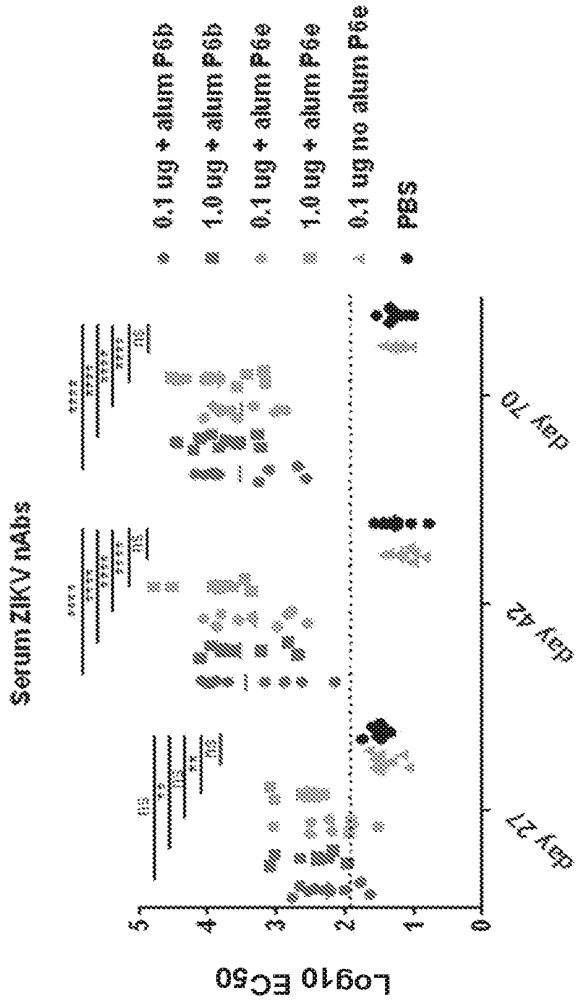


FIG. 13A

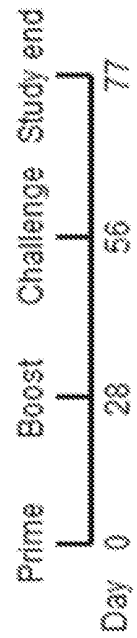


FIG. 13B

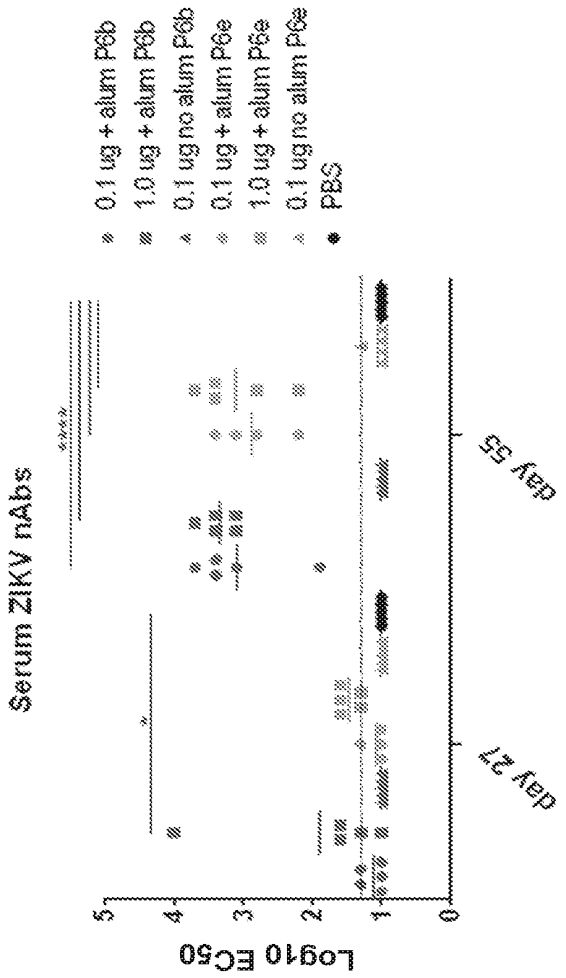


FIG. 14

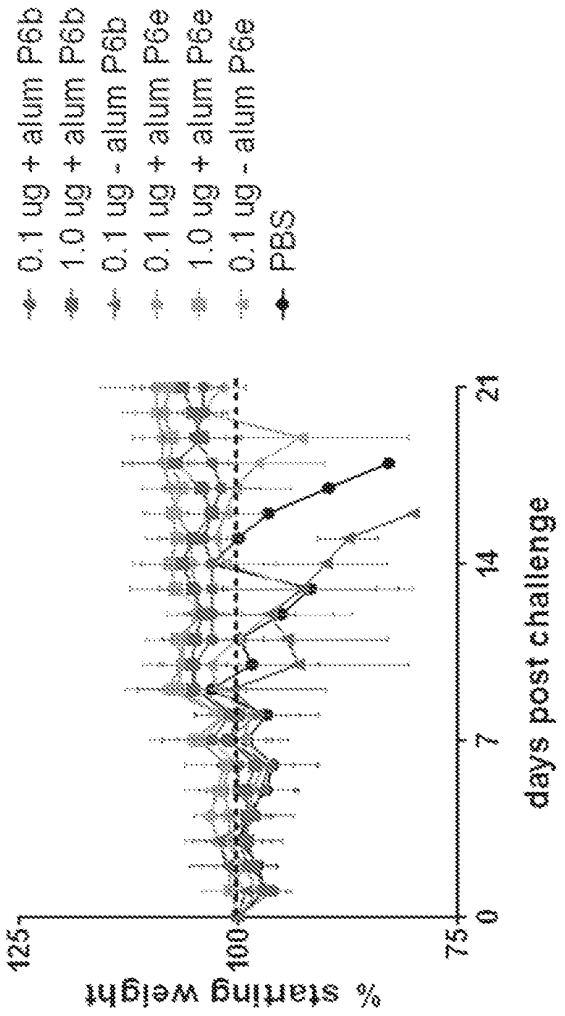

0.1 ug + alum P6b
1.0 ug + alum P6b
0.1 ug - alum P6b
0.1 ug + alum P6e
1.0 ug + alum P6e
0.1 ug - alum P6e
PBS
% starting weight
125
100
75
0
7
14
21
days post challenge

FIG. 15

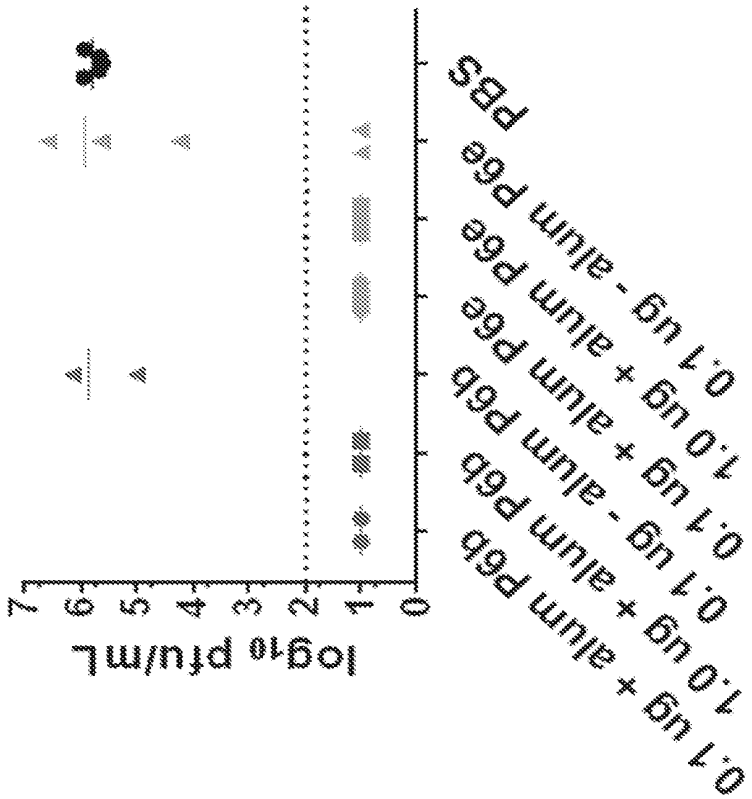

log10 pfu/mL
7
6
5
4
3
2
1
0
0.1 ug + alum P6b
1.0 ug + alum P6b
0.1 ug - alum P6b
0.1 ug + alum P6e
1.0 ug + alum P6e
0.1 ug - alum P6e
PBS

FIG. 16

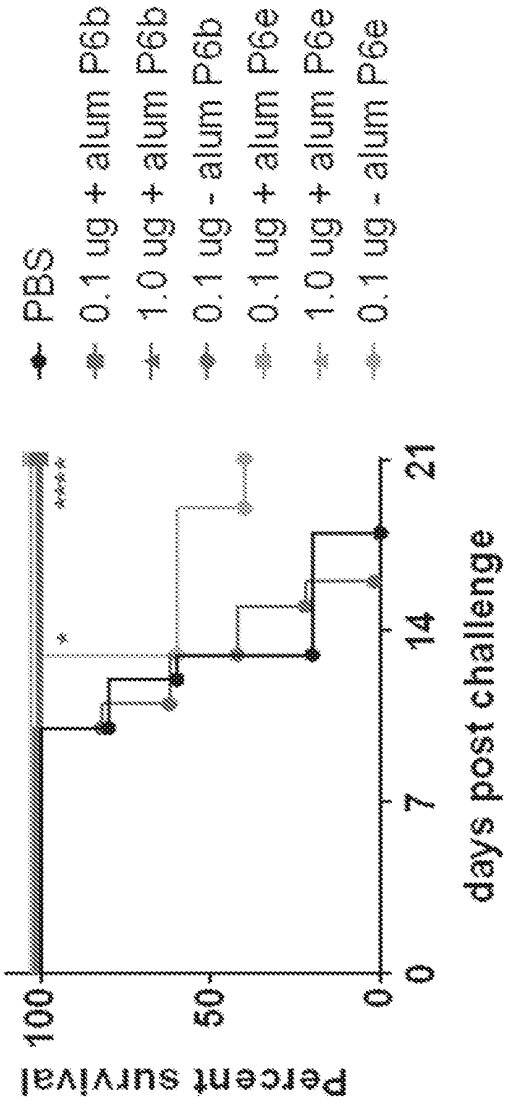

PBS
0.1 ug + alum P6b
1.0 ug + alum P6b
0.1 ug - alum P6b
0.1 ug + alum P6e
1.0 ug + alum P6e
0.1 ug - alum P6e
Percent survival
100
50
0
0
7
14
21
days post challenge
****
*

FIG. 17

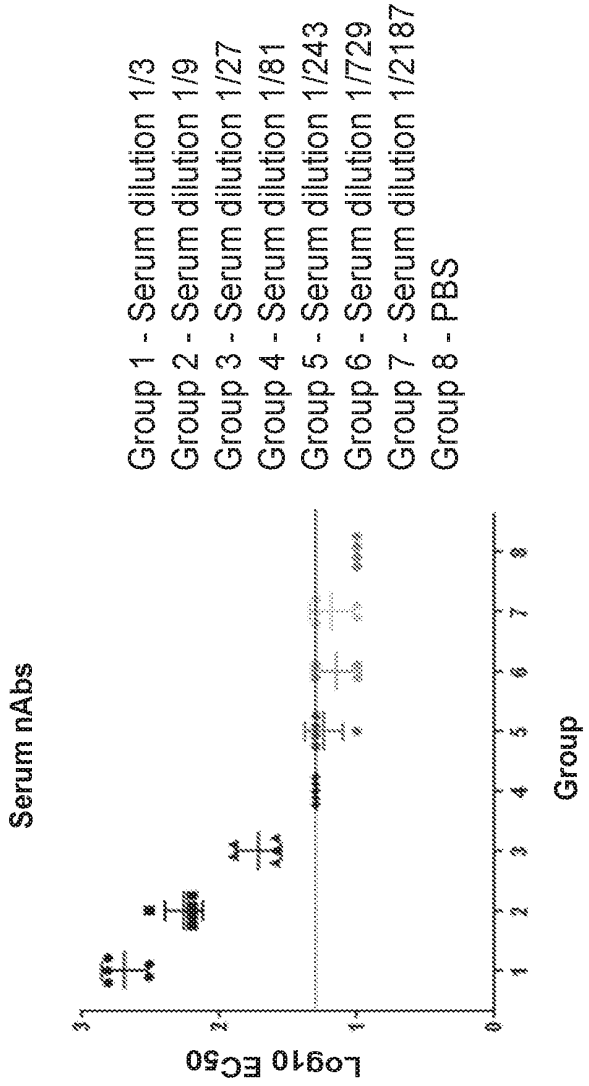

Serum nAbs
Log10 EC50
Group
Group 1 - Serum dilution 1/3
Group 2 - Serum dilution 1/9
Group 3 - Serum dilution 1/27
Group 4 - Serum dilution 1/81
Group 5 - Serum dilution 1/243
Group 6 - Serum dilution 1/729
Group 7 - Serum dilution 1/2187
Group 8 - PBS

FIG. 18

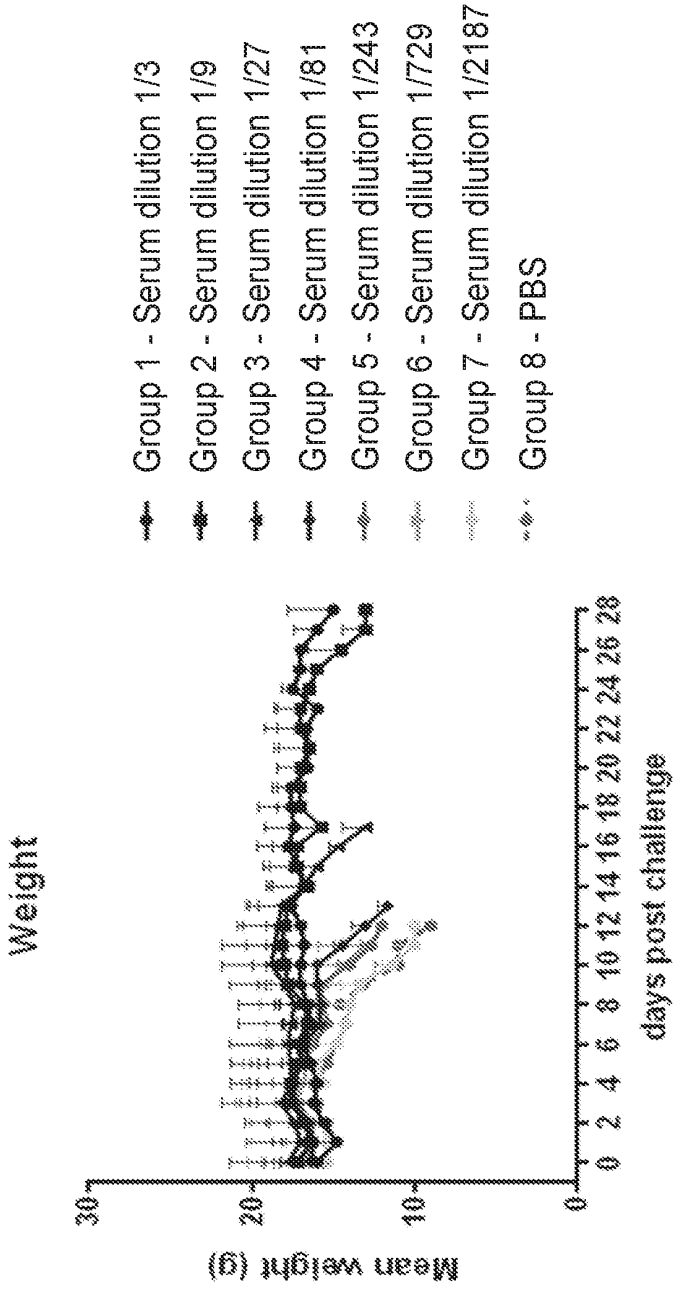

Weight
Mean weight (g)
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
days post challenge
Group 1 - Serum dilution 1/3
Group 2 - Serum dilution 1/9
Group 3 - Serum dilution 1/27
Group 4 - Serum dilution 1/81
Group 5 - Serum dilution 1/243
Group 6 - Serum dilution 1/729
Group 7 - Serum dilution 1/2187
Group 8 - PBS

FIG. 19

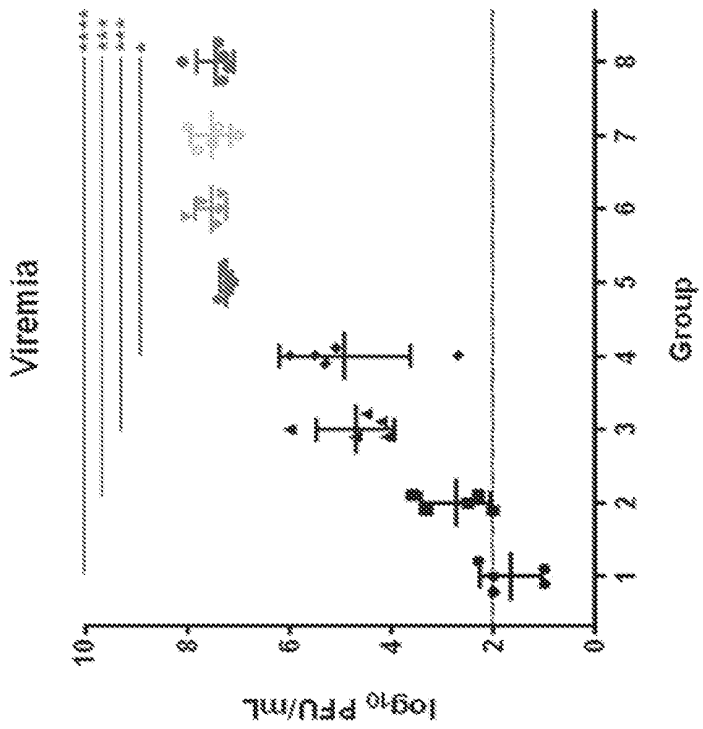

Viremia
Group 1 - Serum dilution 1/3
Group 2 - Serum dilution 1/9
Group 3 - Serum dilution 1/27
Group 4 - Serum dilution 1/81
Group 5 - Serum dilution 1/243
Group 6 - Serum dilution 1/729
Group 7 - Serum dilution 1/2187
Group 8 - PBS
log10 PFU/mL
Group
0
2
4
6
8
10
1
2
3
4
5
6
7
8

FIG. 20

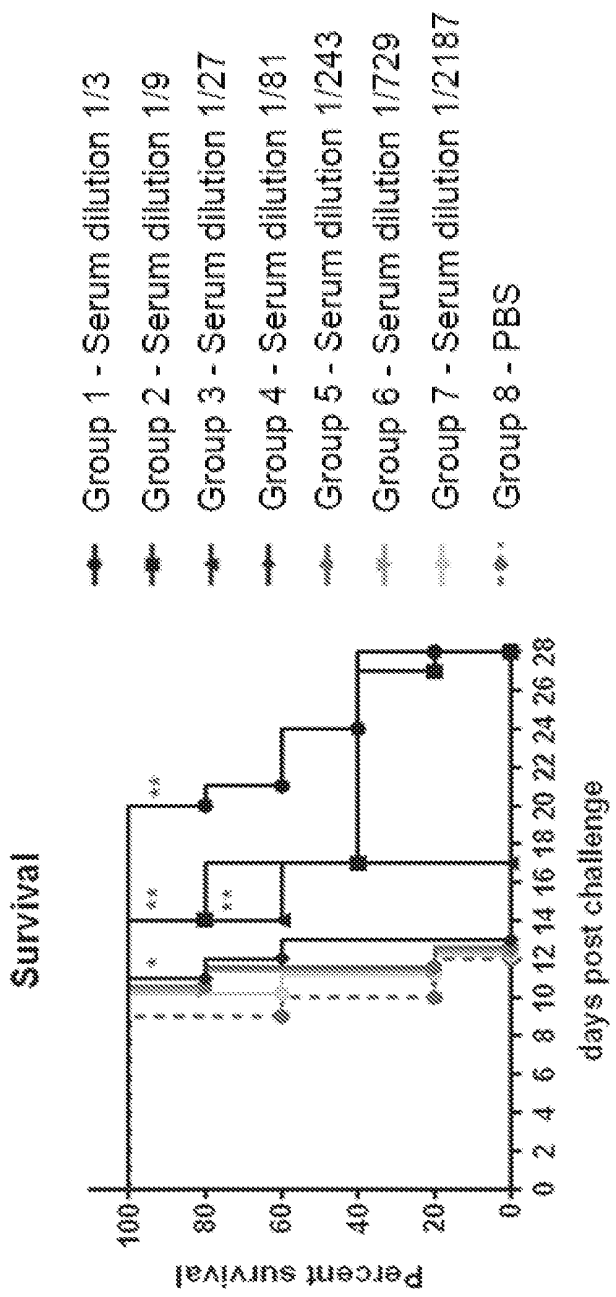

Survival
Percent survival
days post challenge
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
0 20 40 60 80 100
*
**
**
**
Group 1 - Serum dilution 1/3
Group 2 - Serum dilution 1/9
Group 3 - Serum dilution 1/27
Group 4 - Serum dilution 1/81
Group 5 - Serum dilution 1/243
Group 6 - Serum dilution 1/729
Group 7 - Serum dilution 1/2187
Group 8 - PBS

FIG. 21

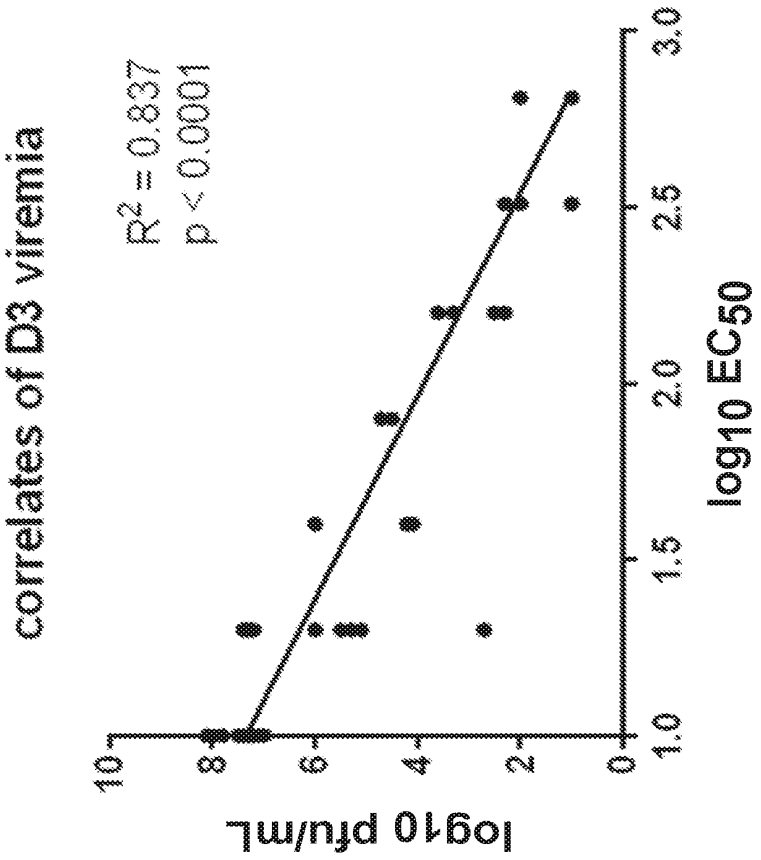

correlates of D3 viremia
$R^2 = 0.837$
$p < 0.0001$
log10 pfu/mL
10
8
6
4
2
0
log10 EC50
1.0
1.5
2.0
2.5
3.0

FIG. 22

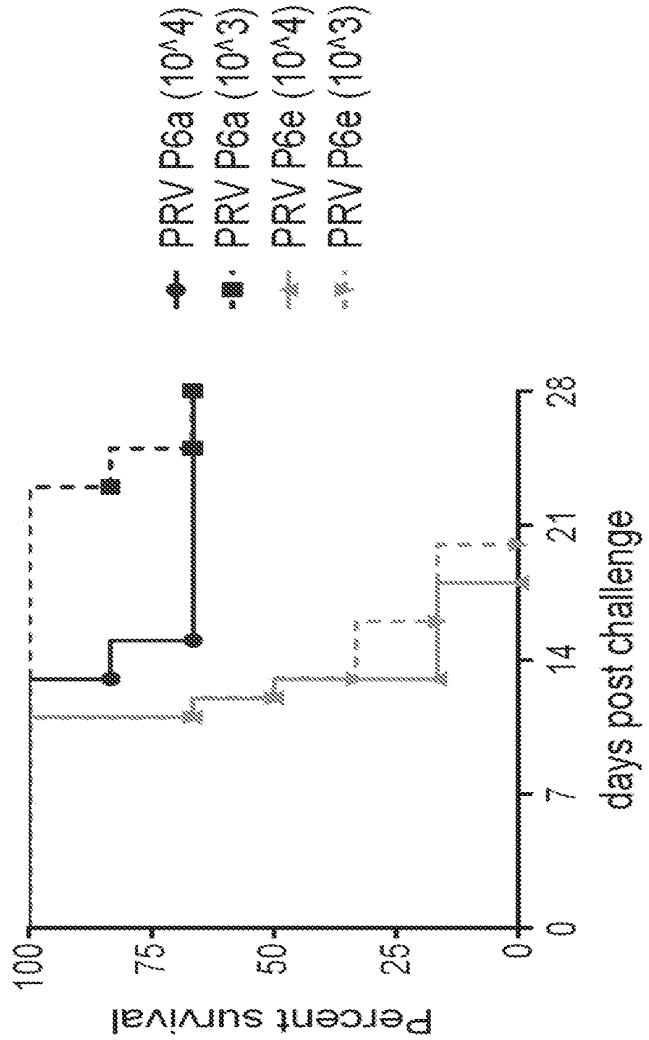

PRV P6a (10^4)
PRV P6a (10^3)
PRV P6e (10^4)
PRV P6e (10^3)
Percent survival
100
75
50
25
0
0
7
14
21
28
days post challenge

FIG. 23

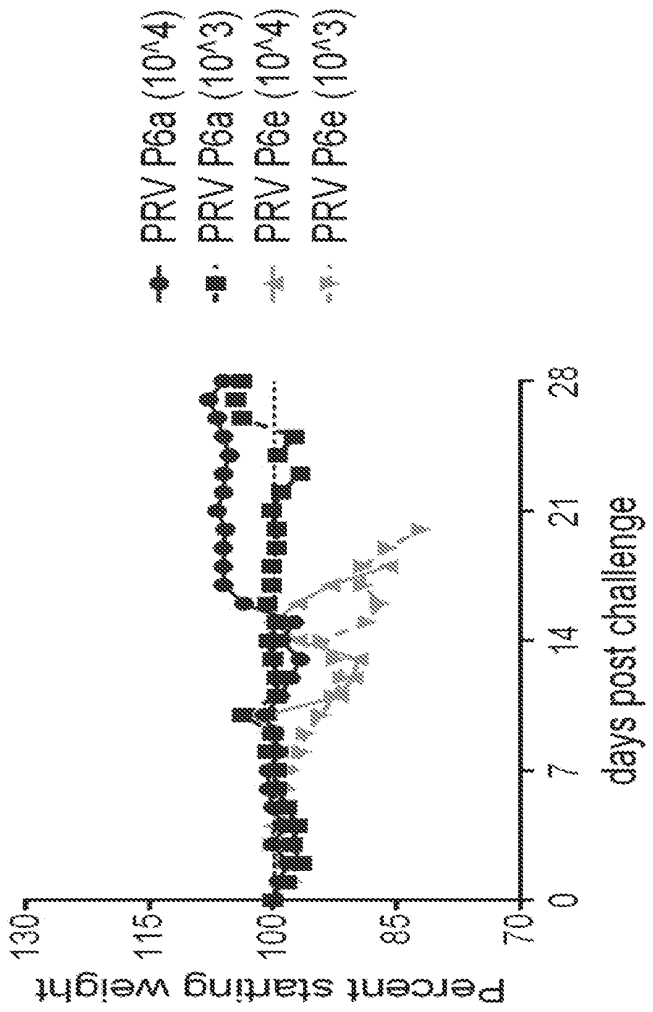

PRV P6a (10^4)
PRV P6a (10^3)
PRV P6e (10^4)
PRV P6e (10^3)
Percent starting weight
130
115
100
85
70
0
7
14
21
28
days post challenge

FIG. 24

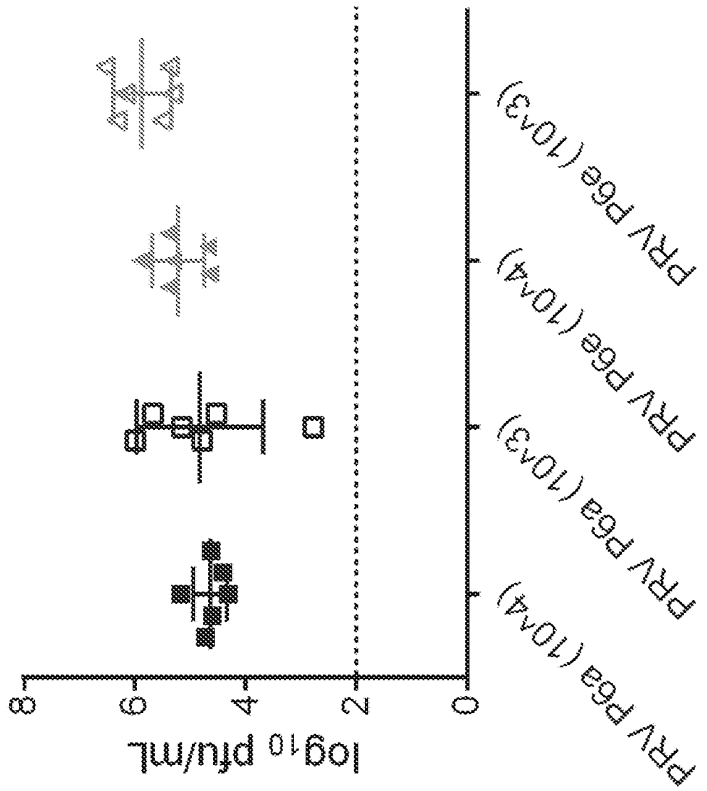

log10 pfu/mL
8
6
4
2
0
PRV Pβa (10^4)
PRV Pβa (10^3)
PRV Pβe (10^4)
PRV Pβe (10^3)

FIG. 25

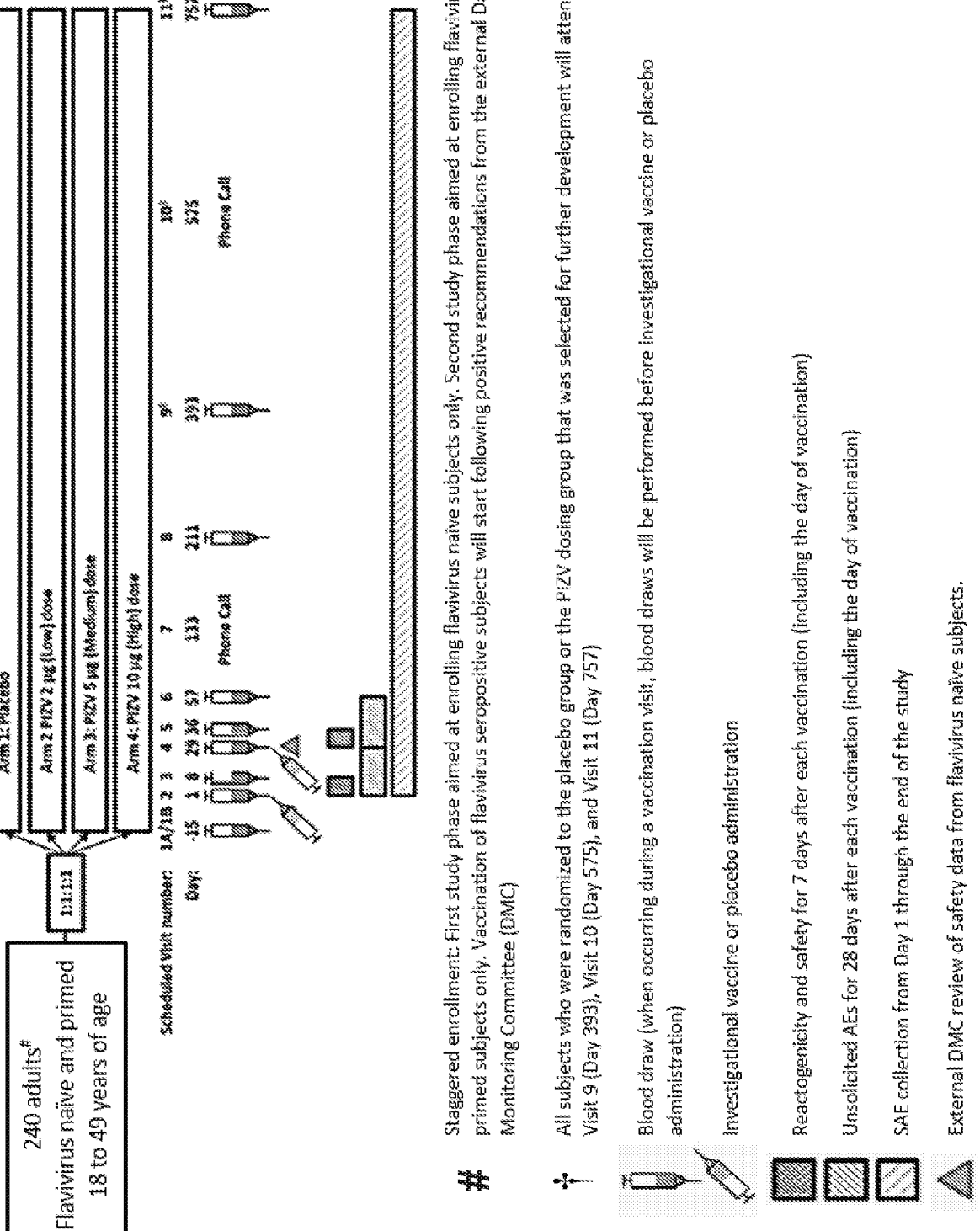

Schematic Representation of Trial Design
240 adults#
Flavivirus naïve and primed
18 to 49 years of age
1:1:1:1
Arm 1: Placebo
Arm 2: PIZV 2 µg (Low) dose
Arm 3: PIZV 5 µg (Medium) dose
Arm 4: PIZV 10 µg (High) dose
Scheduled Visit number: 1A/1B 2 3 4 5 6 7 8 9† 10† 11†
Day: -15 1 8 29 36 57 133 211 393 575 757
Phone Call
Phone Call
Staggered enrollment: First study phase aimed at enrolling flavivirus naïve subjects only. Second study phase aimed at enrolling flavivirus primed subjects only. Vaccination of flavivirus seropositive subjects will start following positive recommendations from the external Data Monitoring Committee (DMC)
All subjects who were randomized to the placebo group or the PIZV dosing group that was selected for further development will attend Visit 9 (Day 393), Visit 10 (Day 575), and Visit 11 (Day 757)
Blood draw (when occurring during a vaccination visit, blood draws will be performed before investigational vaccine or placebo administration)
Investigational vaccine or placebo administration
Reactogenicity and safety for 7 days after each vaccination (including the day of vaccination)
Unsolicited AEs for 28 days after each vaccination (including the day of vaccination)
SAE collection from Day 1 through the end of the study
External DMC review of safety data from flavivirus naïve subjects.

FIG. 26

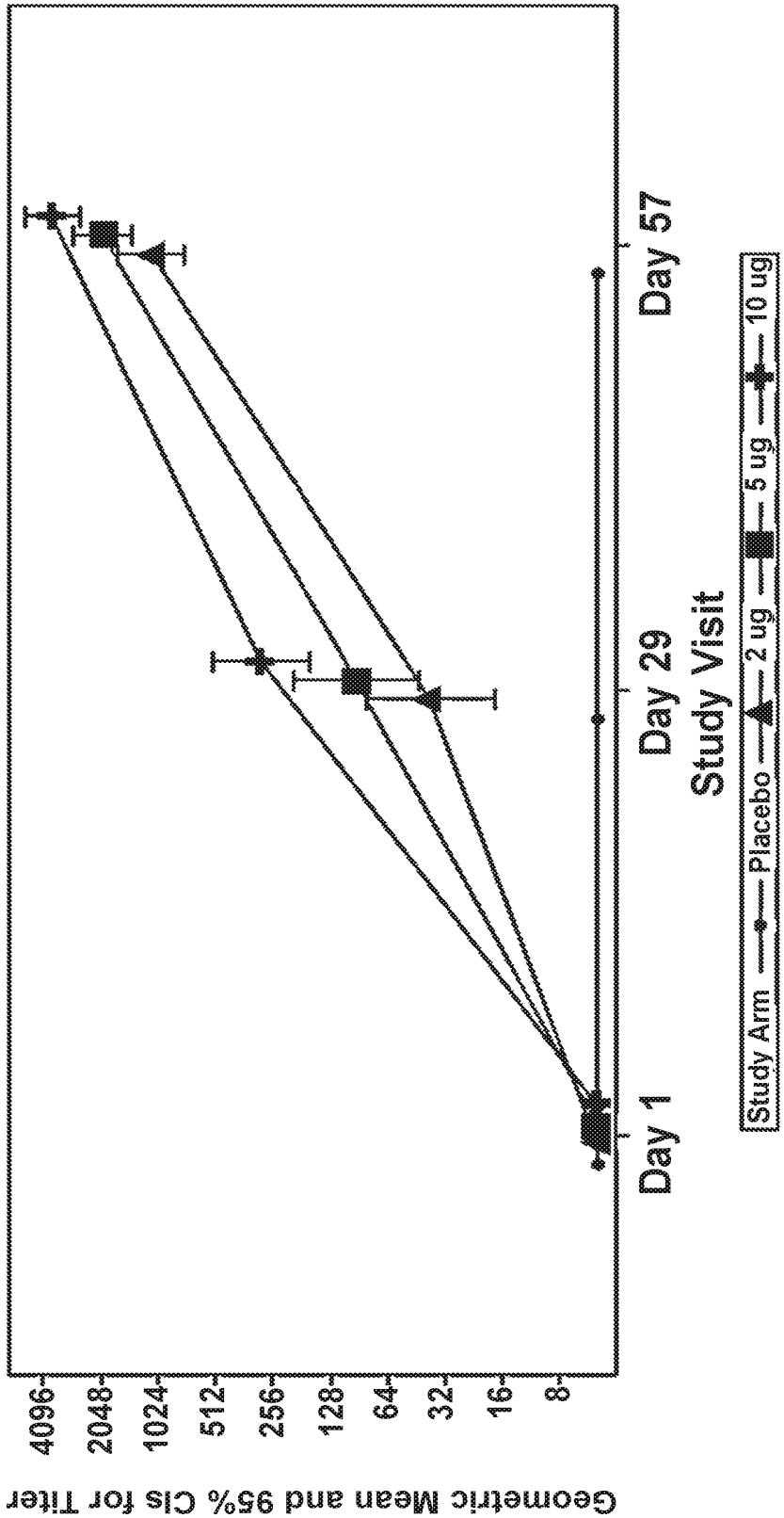

Cohort: FV Naive
Geometric Mean and 95% CIs for Titer
4096
2048
1024
512
256
128
64
32
16
8
Day 1
Day 29
Day 57
Study Visit
Study Arm
Placebo
2 ug
5 ug
10 ug

FIG. 27

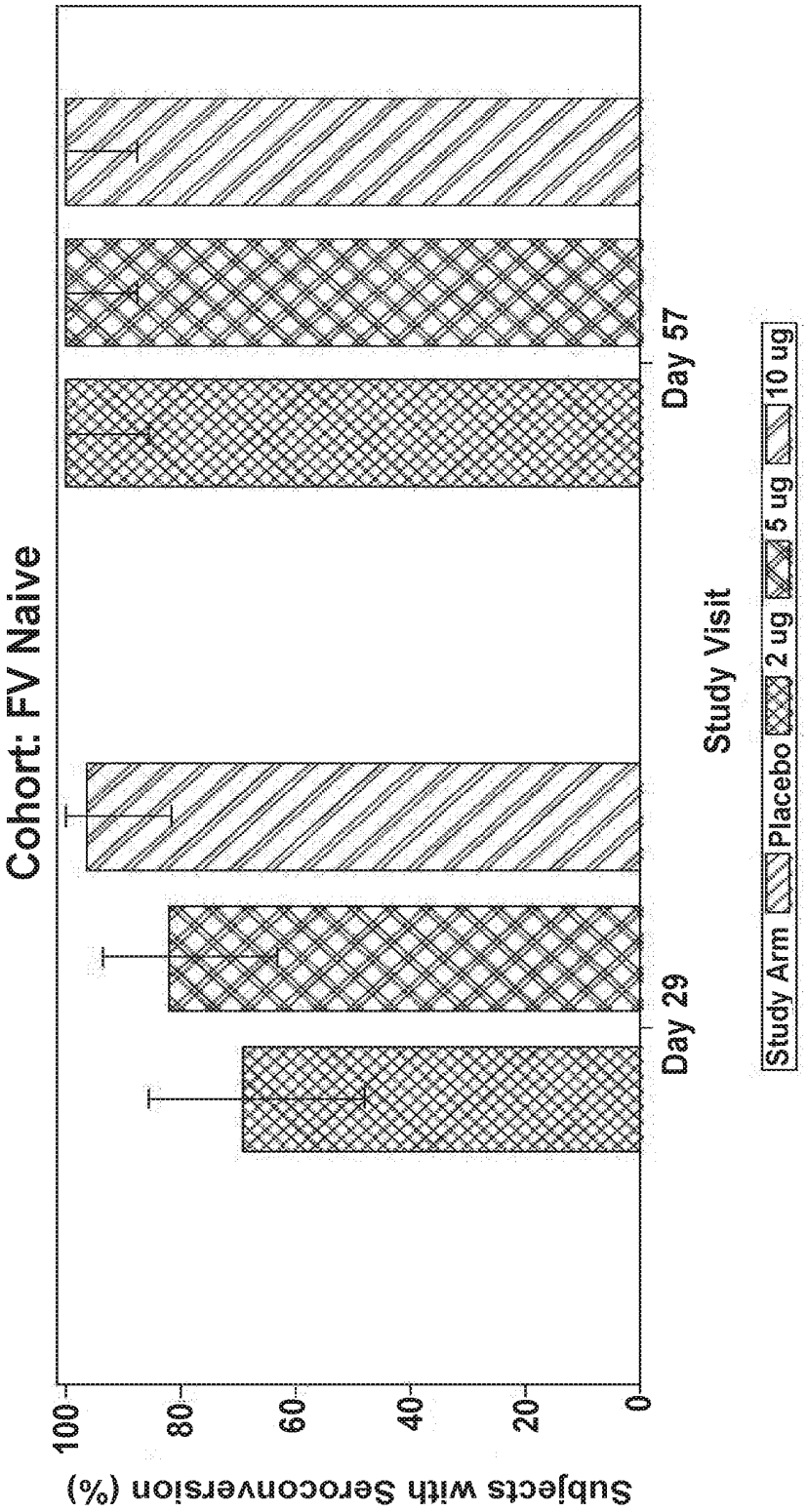

Cohort: FV Naive
Subjects with Seroconversion (%)
100
80
60
40
20
0
Day 29
Day 57
Study Visit
Study Arm
Placebo
2 ug
5 ug
10 ug

FIG. 28

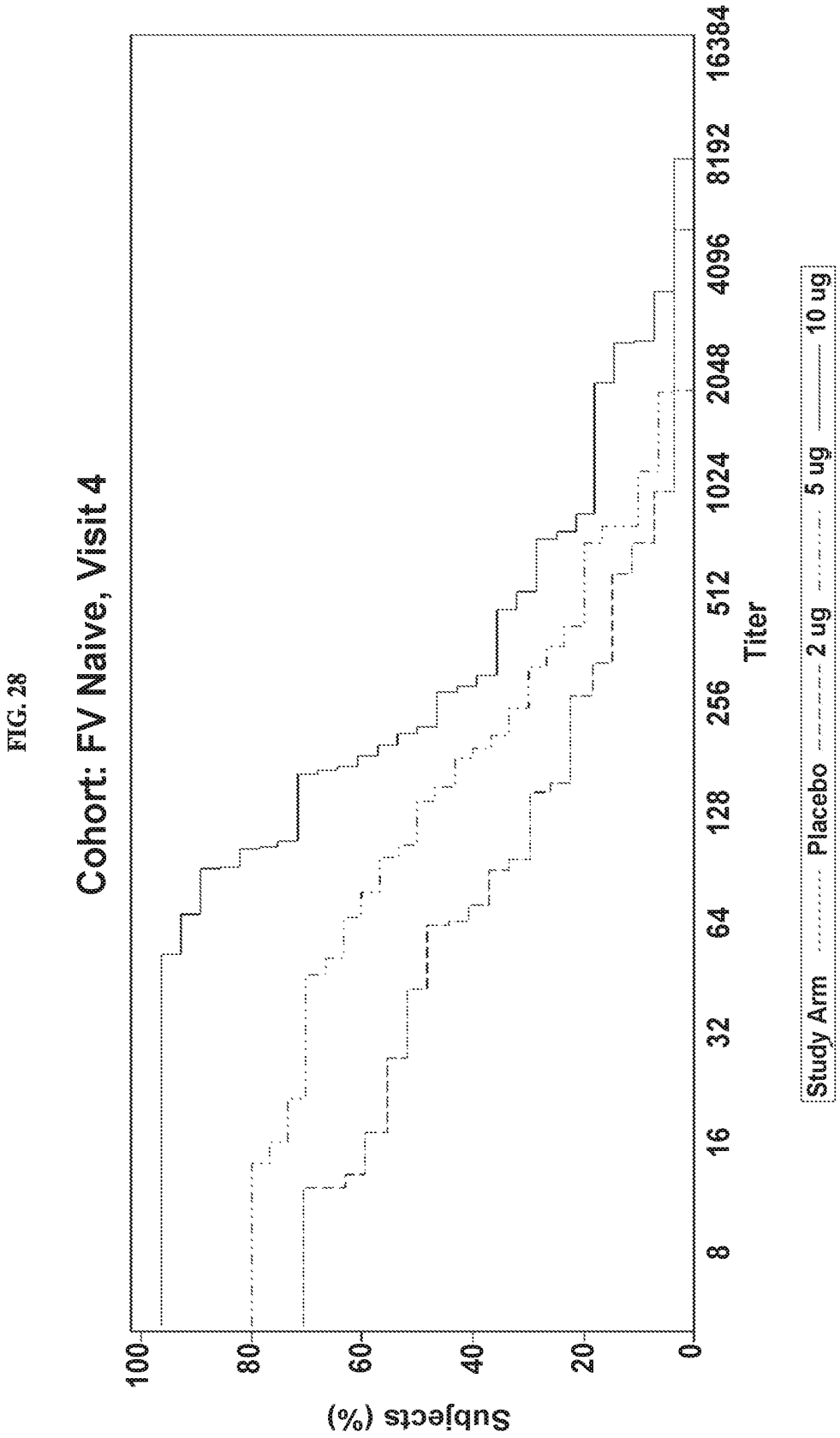
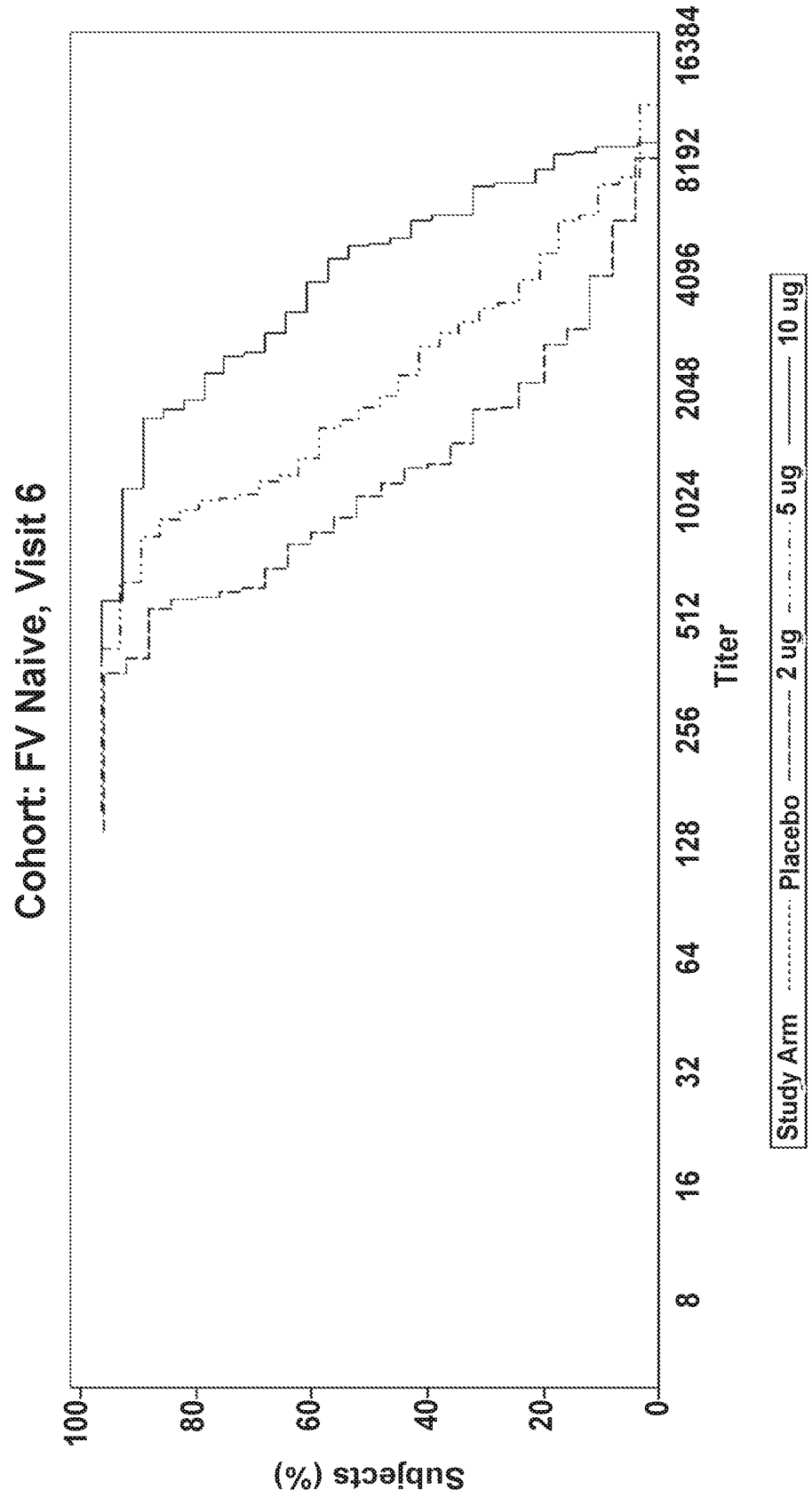

Cohort: FV Naive, Visit 4
Subjects (%)
100
80
60
40
20
0
8
16
32
64
128
256
512
1024
2048
4096
8192
16384
Titer
Study Arm
Placebo
2 ug
5 ug
10 ug

FIG. 29


Cohort: FV Naive, Visit 6
Subjects (%)
100
80
60
40
20
0
8
16
32
64
128
256
512
1024
2048
4096
8192
16384
Titer
Study Arm
Placebo
2 ug
5 ug
10 ug

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

SCHUBERT, Michael J.
Leydig, Voit & Mayer, Ltd.
Two Prudential Plaza – Suite 4900
180 North Stetson Avenue
Chicago, Illinois 60601-6731
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing *(day/month/year)*
30 April 2020 (30.04.2020)

Applicant's or agent's file reference
741065

IMPORTANT NOTIFICATION

International application No.
PCT/US2018/059233

International filing date *(day/month/year)*
05 November 2018 (05.11.2018)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES
Office of Technology Transfer, National Institutes of Health
5601 Fishers Lane, Rm. 2G36, MSC 9804
Rockville, Maryland 20892
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address: docketingpatent@leydig.com

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

State of Nationality:
State of Residence:
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:
The person identified in Box 1 has been deleted from the records.

4. A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer
Moussaid El Mostafa
e-mail pct.team6@wipo.int
Telephone No. +41 22 338 74 06

Form PCT/IB/306 (January 2009) I/HRFGS6W9LXPT60

Mail Stop PCT
Attorney Docket: 38011U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

LIVENGOOD, et al.		Conf. No.:	TBD
Appl. No.:	Not Yet Assigned	Examiner:	TBD
Filed:	May 5, 2020	Art Unit:	TBD
Intl. Appl. No.:	PCT/US2018/059233		
Intl. Filing Date:	November 5, 2018		

Title: **ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS USING THE SAME**

PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Prior to examination on the merits and calculating the filing fees for the national phase application under 35 U.S.C. 371, filed herewith, please enter the following amendments:

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims begin on page 3 of this paper.

Remarks begin on page 6 of this paper.

A **Conclusion** appears at page 7 of this paper.

Amendments to the Specification:

On page 1 of the Specification, please insert a cross-reference to a prior application after the title and before the heading of the first paragraph by adding the following:

-- This is a National Phase Application filed under 35 U.S.C. 371 as a national stage of PCT/US2018/059233, filed November 5, 2018, an application claiming the benefit of U.S. Provisional Application No. 62/581,500, filed November 3, 2017 and U.S. Provisional Application No. 62/592,995, filed November 30, 2017, the content of each of which is hereby incorporated by reference in its entirety. --

Please insert the following reference to the incorporated Sequence Listing in text format immediately after the paragraph titled "Field of Invention", as following:

The Sequence Listing submitted in text format (.txt) on April 28, 2020, named "SequenceListingaspublished.txt", (created on Friday, April 24, 2020, 25KB), is incorporated herein by reference.

Please enter the twelve (14) pages of Sequence Listing in text format attached hereto into the Specification after the Abstract and before the Drawings.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

Claims 1-54 (Canceled)

55. (New) A vaccine or immunogenic composition comprising a dose of 1µg to 40µg of one antigen from a Zika virus, wherein the antigen is an inactivated whole virus.

56. (New) A vaccine or immunogenic composition of claim 55, the Zika virus having a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

57. (New) The vaccine or immunogenic composition of claim 55, wherein the antigen is purified.

58. (New) The vaccine or immunogenic composition of claim 57, wherein the main peak of the purified antigen in a size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

59. (New) The vaccine or immunogenic composition of claim 55, wherein the vaccine or immunogenic composition comprises a dose of about 10µg of purified inactivated whole virus.

60. (New) The vaccine or immunogenic composition of claim 56, wherein the at least one mutation is a Trp98Gly mutation.

61. (New) The vaccine or immunogenic composition of claim 55, wherein the Zika virus is from strain PRVABC59.

62. (New) The vaccine or immunogenic composition of claim 55, wherein the vaccine or immunogenic composition comprises 100 µg to 600µg aluminum hydroxide.

63. (New) The vaccine of claim 55, wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.

64. (New) The vaccine or immunogenic composition of claim 55 comprising

- a dose of about 10µg of purified inactivated whole virus
- about 200 µg aluminum hydroxide,
- a buffer; and optionally
- a sugar such as sucrose.

65. (New) A method of treating or preventing, in particular preventing Zika virus infection in a subject in need thereof, comprising administering to the subject the vaccine or immunogenic composition of claim 55.

66. (New) The method of any one of claim 65, wherein the subject is pregnant or intends to become pregnant or is a woman of childbearing potential.

67. (New) The method of claim 65, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.

68. (New) The method of claim 65, wherein the vaccine or immunogenic composition is administered one or more times.

69. (New) The method of claim 65, wherein the vaccine or immunogenic composition comprising a dose of 10µg is administered one time.

70. (New) The method of claim 65, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration.

71. (New) The method of claim 70, wherein the prime and boost administration takes place from about 1 to about 16 weeks apart.

72. (New) The method of claim 70, wherein the second (boost) administration is administered at least 28 days after the first (prime) administration.

73. (New) The method of claim 70, wherein 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 1000, or of greater than 1500, or of greater than 2000, or of greater than 3000 are induced, as determined by the plaque reduction neutralization test (PRNT).

REMARKS

The specification has been amended to incorporate by reference to the earlier filed application.

The Sequence Listing is submitted via EFS-Web as ASCII compliant text file (.txt) only and serves as a paper copy of the Sequence Listing required by 37 C.F.R. § 1.821(c) and the Sequence Listing in computer-readable form (CRF) required by 37 C.F.R. § 1.821(e). A statement under 37 C.F.R. § 1.821(f) is therefore not necessary. The amendment entering the Sequence Listing into the application is in accordance with the relevant sections of 37 C.F.R. §§ 1.821-1.825 and does not include any new matter within the meaning of 35 U.S.C. § 132.

Amendments to the claims have been presented to reduce excess claim fees and to conform them to U.S. practice. Upon entry of the above amendments, claims 1-54 are canceled and claims 55-73 have been added. Claims 55-73 are pending in this application. The claim amendments do not introduce new matter within the meaning of 35 U.S.C. §132.

Applicant reserves the right to reintroduce any cancelled subject matter to this application or to any child applications, or to reintroduce the full scope of any claim amended herein.

Accordingly, the Examiner is respectfully requested to enter the above amendments before examination. Favorable consideration is requested.

CONCLUSION

The Examiner is welcomed to telephone the undersigned attorney on any questions or comments that may arise.

In the event this paper is not timely filed, Applicant hereby petitions for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

NATH, GOLDBERG & MEYER

Date: May 4, 2020

/Joshua B. Goldberg/

Joshua B. Goldberg, Reg. No. 44126
Customer No.: 20529

NATH, GOLDBERG & MEYER
112 S. West Street, Alexandria, VA 22314
TEL: (703) 548-6284; FAX: (703) 683-8396
JBG/als

PTO/AIA/14 (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	38011U
	Application Number	
Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jill	A	LIVENGOOD	

Residence Information (Select One) ● US Residency Non US Residency Active US Military Service

City	Cambridge	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Takeda Vacines, Inc.
Address 2	75 Sidney Street

City	Cambridge	State/Province	MA
Postal Code	02139	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Hansi		DEAN	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

City	Cambridge	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	Vaccine Business Unit, Takeda Phamaceuticals
Address 2	40 Landsdowne Street

City	Cambridge	State/Province	MA
Postal Code	02139	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Htay	Htay	HAN	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	38011U
	Application Number	
Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME	

City	Cambridge	State/Province	MA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	c/o Takeda Vaccines, Inc.
Address 2	40 Landsdowne Street

City	Cambridge	State/Province	MA
Postal Code	02139	Country i	US

Inventor 4 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Raman		RAO	

Residence Information (Select One) ○ US Residency ● Non US Residency Active US Military Service

City	Singapore	Country of Residence i	SG

Mailing Address of Inventor:

Address 1	c/o Takeda Vaccines Pte Ltd.
Address 2	21 Biopolis Road; Nucleos North Tower, Level 4

City	Singapore	State/Province	
Postal Code	138567	Country i	SG

Inventor 5 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jackie		MARKS	

Residence Information (Select One) ○ US Residency ◉ Non US Residency Active US Military Service

City	Cambridge	Country of Residence i	MA

Mailing Address of Inventor:

Address 1	c/o Takeda Vaccines, Inc.
Address 2	40 Landsdowne Street

City	Cambridge	State/Province	
Postal Code	02139	Country i	MA

Inventor 6 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Gary		DUBIN	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	38011U
	Application Number	
Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME	

Residence Information (Select One) ○ US Residency ◉ Non US Residency Active US Military Service

City	Glattpark-Opfikon, Zurich	Country of Residence [i]	CH

Mailing Address of Inventor:

Address 1	c/o Takeda Pharmaceutical International AG		
Address 2	Thurgauerstrasse 130		
City	Glattpark-Opfikon, Zurich	State/Province	
Postal Code	8152	Country [i]	CH

Inventor 7 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Laurence		DE MOERLOOZE	

Residence Information (Select One) ○ US Residency ◉ Non US Residency Active US Military Service

City	Glattpark-Opfikon, Zurich	Country of Residence [i]	CH

Mailing Address of Inventor:

Address 1	c/o Takeda Pharmaceutical International AG		
Address 2	Thurgauerstrasse 130		
City	Glattpark-Opfikon, Zurich	State/Province	
Postal Code	8152	Country [i]	CH

Inventor 8 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Hetal		PATEL	

Residence Information (Select One) ◉ US Residency ○ Non US Residency Active US Military Service

City	Cambridge	State/Province	MA	Country of Residence [i]	US

Mailing Address of Inventor:

Address 1	c/o Takeda Vaccines, Inc.		
Address 2	40 Landsdowne Street		
City	Cambridge	State/Province	MA
Postal Code	02139	Country [i]	US

Inventor 9 Remove

Legal Name

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	38011U
	Application Number	
Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sushma		KOMMAREDDY	

Residence Information (Select One) ◉ US Residency ○ Non US Residency Active US Military Service

City	Cambridge	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Takeda Vaccines, Inc.
Address 2	40 Landsdowne Street

City	Cambridge	State/Province	
Postal Code	02139	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	20529		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME		
Attorney Docket Number	38011U	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	29	Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	38011U
	Application Number	
Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	◯ Limited Recognition (37 CFR 11.9)
Customer Number	20529		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	a 371 of international	PCT/US2018/059233	2018-11-05
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2018/059233	Claims benefit of provisional	62581500	2017-11-03
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2018/059233	Claims benefit of provisional	62592995	2017-11-30

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	38011U
	Application Number	
Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME	

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	38011U
	Application Number	
Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	38011U
	Application Number	
Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	TAKEDA VACCINES, INC.		
Mailing Address Information For Applicant:			
Address 1	75 Sidney Street		
Address 2			
City	Cambridge	**State/Province**	
Country	MA	Postal Code	02139
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Approved for use through 11/30/2020. OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	38011U
	Application Number	
Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Joshua B. Goldberg/			Date (YYYY-MM-DD)	2020-05-04
First Name	Joshua	Last Name	Goldberg	Registration Number	44126

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	38011U
	Application Number	
Title of Invention	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO-1390 (01-18)
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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

Attorney Docket No.	
38011U	
U.S. Application No. (if known, see 37 CFR 1.5)	

International Application No.	International Filing Date	Priority Date Claimed
PCT/US2018/059233	05 November 2018 (05.11.2018)	03 November 2017 (03.11.2017)

Title of Invention
ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME

First Named Inventor
Jill A. LIVENGOOD

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ■ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). NOTE: The express request under 35 U.S.C. 371(f) will not be effective unless the requirements under 35 U.S.C. 371(c)(1), (2), and (4) for payment of the basic national fee, copy of the International Application and English translation thereof (if required), and the oath or declaration of the inventor(s) have been received.
2. ■ A copy of the International Application (35 U.S.C. 371(c)(2)) is attached hereto (not required if the International Application was previously communicated by the International Bureau or was filed in the United States Receiving Office (RO/US)).
3. An English language translation of the International Application (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
4. An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))
   a. ☐ is attached.
   b. ☐ was previously filed in the international phase under PCT Rule 4.17(iv).

Items 5 to 8 below concern amendments made in the international phase.

PCT Article 19 and 34 amendments

5. ☐ Amendments to the claims under PCT Article 19 are attached (not required if communicated by the International Bureau) (35 U.S.C. 371(c)(3)).
6. ☐ English translation of the PCT Article 19 amendment is attached (35 U.S.C. 371(c)(3)).
7. ☐ English translation of annexes (Article 19 and/or 34 amendments only) of the International Preliminary Examination Report is attached (35 U.S.C. 371(c)(5)).

Cancellation of amendments made in the international phase

8a. ☐ Do not enter the amendment made in the international phase under PCT Article 19.

8b. ☐ Do not enter the amendment made in the international phase under PCT Article 34.

NOTE: A proper amendment made in English under Article 19 or 34 will be entered in the U.S. national phase application absent a clear instruction from applicant not to enter the amendment(s).

The following items 9 to 17 concern a document(s) or information included.

9. ■ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
10. ■ A preliminary amendment.
11. ■ An Application Data Sheet under 37 CFR 1.76.
12. ☐ A substitute specification. NOTE: A substitute specification cannot include claims. See 37 CFR 1.125(b).
13. ☐ A power of attorney and/or change of address letter.
14. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.3 and 37 CFR 1.821-1.825 (not required if sequence listing in text format was indicated on the PCT Request as part of the International Application and the sequence listing was published as part of the international application).
15. ☐ Assignment papers *(cover sheet and document(s))*. Name of Assignee: TAKEDA VACCINES, INC.
16. ☐ 37 CFR 3.73(c) Statement *(when there is an Assignee)*.

This collection of information is required by 37 CFR 1.414 and 1.491-1.492. The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 15 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

U.S. APPLN. No. (if known – see 37 CFR 1.5)	INTERNATIONAL APPLICATION No.	ATTORNEY DOCKET No.
	PCT/US2018/059233	38011U

17. [X] Other items or information:

Front page of International Publication
PCT/IB/306
Nine (9) unexecuted Declarations

The following fees have been submitted.	CALCULATIONS
18. [■] Basic national fee (37 CFR 1.492(a)) **$300**	$ 300
19. [■] Examination fee (37 CFR 1.492(c)) • If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4)..... **$0** • All other situations **$760**	$ 760
20. [■] Search fee (37 CFR 1.492(b)) • If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4)..... **$0** • Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority ..... **$140** • International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB..... **$520** • All other situations **$660**	520 $
TOTAL OF 18, 19, and 20 =	$ 1580
[ ] Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)). Fee for each additional 50 sheets of paper or fraction thereof **$400**	800

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round **up** to a whole number)	RATE	
186 - 100 =	86 / 50 =	2	x **$400**	$

Surcharge for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h))..... **$140**	$ 140

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	- 20 =		x **$100**	$
Independent claims	- 3 =		x **$460**	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			**+ $820**	$

Fee for submission of Sequence Listing text file of 300 MB to 800 MB (37 CFR 1.21(o)(1))..... **$1,000**	$
Fee for submission of Sequence Listing text file of more than 800 MB (37 CFR 1.21(o)(2))..... **$10,000**	$
Processing fee for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i))..... **$140 +**	$
TOTAL OF ABOVE CALCULATIONS =	$ 2520
[ ] **Applicant asserts small entity status.** See 37 CFR 1.27. Fees above are reduced by ½.	
[ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Fees above are reduced by ¾. Applicant must attach form PTO/SB/15A or B or equivalent.	
TOTAL NATIONAL FEE =	$ 2520
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31)..... **$50.00** per property **+**	$
TOTAL FEES ENCLOSED =	$ 2520

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees.

c. ☐ The Director is hereby authorized to charge additional fees which may be required, or credit any overpayment, to Deposit Account No. _____ as follows:

i. ☐ any required fee.

ii. ☐ any required fee except for excess claims fees required under 37 CFR 1.492(d) and (e) and multiple dependent claim fee required under 37 CFR 1.492(f).

d. ■ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

ADVISORY: If filing by EFS-Web, do **NOT** attach the PTO-2038 form as a PDF along with your EFS-Web submission. Please be advised that this is **not** recommended and by doing so your **credit card information may be displayed via PAIR**. To protect your information, it is recommended to pay fees online by using the electronic payment method.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013, and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE 1: By providing this statement under 37 CFR 1.55 or 1.78, **this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA**.

NOTE 2: A U.S. national stage application may not claim priority to the international application of which it is the national phase. The filing date of a U.S. national stage application is the international filing date. See 35 U.S.C. 363.

Correspondence Address

■ The address associated with Customer Number: 20529 **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone			
Email					

Signature	/Joshua B. Goldberg/	Date	2020-05-04
Name (Print/Type)	Joshua B. Goldberg	Registration No. (Attorney/Agent)	44126

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME
First Named Inventor/Applicant Name:	Jill A. LIVENGOOD
Filer:	Stanley Protigal/Amanda Suazo
Attorney Docket Number:	38011U

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
NATIONAL STAGE FEE	1631	1	300	300
NATL STAGE SEARCH FEE - REPORT PROVIDED	1642	1	520	520
NATIONAL STAGE EXAM - ALL OTHER CASES	1633	1	760	760
Pages:				
NATL STAGE APPL SZ FEE PER 50 PGS >100	1681	2	400	800
Claims:				
Miscellaneous-Filing:				
OATH/DECL > 30 MOS FROM 371 COMMENCEMENT	1617	1	140	140

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	2520

Electronic Acknowledgement Receipt	
EFS ID:	39329672
Application Number:	16761329
International Application Number:	PCT/US2018/059233
Confirmation Number:	5672
Title of Invention:	ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME
First Named Inventor/Applicant Name:	Jill A. LIVENGOOD
Customer Number:	20529
Filer:	Stanley Protigal/Amanda Suazo
Filer Authorized By:	Stanley Protigal
Attorney Docket Number:	38011U
Receipt Date:	04-MAY-2020
Filing Date:	
Time Stamp:	14:07:56
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$2520
RAM confirmation Number	E202054E08306379
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		SPEC.pdf	701382 fc2f5ac2de6727fb8fc44726ff38192ea03b9145	yes	143
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	135	
	Claims		136	142	
	Abstract		143	143	
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	IDS.pdf	1007503 10cddfb420a79100f8522ba982d8b2114dba70f4	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Foreign Reference	WO2017109223A1.pdf	3461060 15b098d5f912b678c1a9ded101abb53615f544dc	no	184
Warnings:					
Information:					
4	Non Patent Literature	Baldwin.pdf	3649390 b4381e71e910d790d2557478635d604deea75ec6	no	13
Warnings:					
Information:					

5	Non Patent Literature	Druelle.pdf	2743215 40d17a4241b8c5ba1d7b0855e15fe34f1e149b28	no	12
Warnings:					
Information:					
6	Non Patent Literature	Shan.pdf	1838168 c4275c50a574142f6f756ebf977e4f2392f5b63e	no	8
Warnings:					
Information:					
7	Non Patent Literature	Tiwari.pdf	2605555 2c0641b1e6b72e6d4fbe42fe8bddc11e566eda96	no	10
Warnings:					
Information:					
8	Non Patent Literature	WegerLucarelli.pdf	2328386 d5b94e180e46b52bacd6769684f84fe776b1ebc1	no	12
Warnings:					
Information:					
9	Foreign Reference	WO2017009873.pdf	5368874 99f01ba185de3db8e89f9cfa6af917846767e2fc	no	56
Warnings:					
Information:					
10	Sequence Listing (Text File)	SequenceListingaspublished.txt	24845	no	-
Warnings:					
Information:					
11	Other Reference-Patent/App/Search documents	ISR.pdf	358315 06c1c311f2de7216e900f442fe871206e741c43a	no	3
Warnings:					
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12	Documents submitted with 371 Applications	Frontpage_WO.pdf	295361 cdeb9cfffbd7c60db935405fbde0958dc369dd66	no	2
Warnings:					
Information:					
13	Oath or Declaration filed	USPTO_Declaration_T08289WO3-ES_DEAN_38011U.pdf	150300 a6929968e02fd39050f52f0d9831ab150a142080	no	2
Warnings:					
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14	Oath or Declaration filed	USPTO_Declaration_T08289WO3-ES_DUBIN_38011U.pdf	150293 590b8be53feb5436a836a19adfefa5531974f78b	no	2
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15	Oath or Declaration filed	USPTO_Declaration_T08289WO3-ES_HAN_38011U.pdf	150296 84e1ff9f5279e02065c6453adf1c0bde780c260f	no	2
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17	Oath or Declaration filed	USPTO_Declaration_T08289WO3-ES_LIIVENGOOD_38011U.pdf	150322 ddb8c8521aa7d30c7f3128879c877a6ecc6df08e	no	2
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18	Oath or Declaration filed	USPTO_Declaration_T08289WO3-ES_MARKS_38011U.pdf	150299 859d59b41aa7c34fbdb9a81d5f3732cd761aa6b2	no	2
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19	Oath or Declaration filed	USPTO_Declaration_T08289WO3-ES_MOERLOOZE_38011U.pdf	150324 ecf13f23eba477d60746a947c7a90e8f08919dcb	no	2
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20	Oath or Declaration filed	USPTO_Declaration_T08289WO3-ES_PATEL_38011U.pdf	150296 cd38f0888fb3cd148889e8311c75911a894d358e	no	2
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21	Oath or Declaration filed	USPTO_Declaration_T08289WO3-ES_RAO_38011U.pdf	150292 34c18c6ab272d695b4a210e889ce0e15cb733ebc	no	2
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22	Drawings-only black and white line drawings	DRAWINGS.pdf	1120113 c6ecd7755d08c041c327762683cebb3c08dd2a77	no	29
Warnings:					
Information:					
23	Documents submitted with 371 Applications	PCTIB306.pdf	112240 0a5d26a94301ea7bf294530b493261a0e64ed2ab	no	1
Warnings:					
Information:					
24		Template_NationalPhase_PreliminaryAmendment.pdf	43680 fbc4cfca3db4565ed828a0439023774525cf8cf2	yes	7

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
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	Applicant Arguments/Remarks Made in an Amendment		6	7	
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25	Application Data Sheet	ADS.pdf	1794507 0703ab01f3e49a6ee40f431a241fea0c1c54958b	no	11
Warnings:					
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26	Transmittal of New Application	pto1390.pdf	275810 e278934981d3f4f72bfbf5f5226c3d60705d91b4	no	4
Warnings:					
Information:					
27	Fee Worksheet (SB06)	fee-info.pdf	38248 d5412f60e887e660c152911bb0a655fac6cf27f9	no	2
Warnings:					
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		Total Files Size (in bytes):	29119386		

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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ZIKA VACCINES AND IMMUNOGENIC COMPOSITIONS, AND METHODS OF USING THE SAME

STATEMENT REGARDING FEDERALLY-SPONSORED RESEARCH

[0001] This invention was made with government support under Contract No. HHSO100201600015C with the Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority. This invention was created in the performance of a Cooperative Research and Development Agreement with the Centers for Disease Control and Prevention, an Agency of the Department of Health and Human Services. The Government of the United States has certain rights in the invention.

FIELD OF THE INVENTION

[0002] The present disclosure relates to Zika virus vaccines and immunogenic compositions having one or more antigens from a Zika virus (e.g., a Zika virus clonal isolate, a non-human cell adapted Zika virus, etc.) and methods of treatment and uses thereof.

BACKGROUND

[0003] Zika virus, a flavivirus classified with other mosquito-borne viruses (e.g., yellow fever, dengue, West Nile, and Japanese encephalitis viruses) within the Flaviviridae family has spread rapidly in a hemispheric-wide epidemic since the virus was introduced into Brazil in 2013. The virus has reached the Central and North Americas, including territories of the United States, consequently now threatening the continental US. Indeed, Zika virus strain PRVABC59 was isolated from serum from a person who had traveled to Puerto Rico in 2015. The genome of this strain has been sequenced at least three times (See Lanciotti et al. Emerg. Infect. Dis. 2016 May;22(5):933-5 and GenBank Accession Number KU501215.1; GenBank Accession Number KX087101.3; and Yun et al. Genome Announc. 2016 Aug 18;4(4) and GenBank Accession Number ANK57897.1).

[0004] Initially isolated in 1947 in Uganda, the virus was first linked to human disease in 1952, and has been recognized sporadically as a cause of mild, self-limited febrile illness in Africa and Southeast Asia (Weaver *et al.* (2016) Antiviral Res. 130:69-80; Faria *et al.* (2016) Science. 352(6283):345-349). However, in 2007, an outbreak appeared in the North

Pacific island of Yap, and then disseminated from island to island across the Pacific, leading to an extensive outbreak in 2013-2014 in French Polynesia, spreading then to New Caledonia, the Cook Islands, and ultimately, to Easter Island. An Asian lineage virus was subsequently transferred to the Western Hemisphere by routes that remain undetermined (Faria *et al.* (2016) Science. 352(6283):345-349). The virus may be transmitted zoonotically by Aedes aegypti, A. albopictus, and possibly by A. hensilli and A. polynieseinsis (Weaver *et al.* (2016) Antiviral Res. 130:69-80). Additionally, it is thought that other vectors for transmitting the virus may exist, and the virus may be transmitted by blood transfusion, transplacentally, and/or through sexual transmission.

[0005] In late 2015, a significant increase in fetal abnormalities (e.g., microcephaly) and Guillain-Barre syndrome (GBS) in areas of widespread Zika virus infection raised alarm that Zika virus might be much more virulent than originally thought, prompting the World Health Organization (WHO) to declare a Public Health Emergency of International Concern (PHEIC) (Heymann *et al.* (2016) Lancet 387(10020): 719-21). Although the WHO has since declared an end to the PHEIC, Zika continues to pose in particular a significant threat for pregnant women and their unborn babies.

[0006] While Zika virus poses a substantial public health threat, no FDA-approved vaccine or treatment currently exists, and the only preventative measures for controlling Zika virus involve managing mosquito populations.

[0007] In recent efforts to characterize a recombinant Zika virus for the development of a potential vaccine, a non-human cell adapted Zika virus was identified that harbors a mutation in the viral Envelope protein at position 330 (Weger-Lucarelli *et al.* (2017) Journal of Virology 91(1): 1-10). The authors of this study found that full-length infectious cDNA clones of Zika virus strain PRVABC59 were genetically unstable when amplified during cloning, and opted to split the viral genome to address the observed instability, developing and applying a two plasmid system. However, a two plasmid system for the development of a Zika vaccine is less desirable.

BRIEF SUMMARY

[0008] Thus, there is a need to develop vaccines and immunogenic compositions for treating and/or preventing Zika virus. Accordingly, certain aspects of the present disclosure

relate a vaccine or immunogenic composition comprising a dose of 1µg to 40µg of one antigen from a Zika virus, wherein the antigen is an inactivated whole virus.

[0009] Accordingly, certain aspects of the present disclosure relate a vaccine or immunogenic composition comprising a dose of 1µg to 40µg of one antigen from a Zika virus, wherein the Zika virus comprises at least one non-human cell adaptation mutation.

[0010] Accordingly, certain aspects of the present disclosure relate a vaccine or immunogenic composition comprising a dose of 1µg to 40µg of one antigen from a Zika virus, the Zika virus having a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

[0011] To meet the above and other needs, the present disclosure is directed, at least in part, to a genetically stable non-human cell adapted Zika virus harboring an adaptation in the Non-structural protein 1 (with a wild-type Envelope protein), allowing for the use of a single virus/viral genome system for vaccine production. The present disclosure is also directed, at least in part, to a Zika virus clonal isolate that is genetically homogenous and/or has been purified away from one or more adventitious agents. Accordingly, the present disclosure provides vaccines and immunogenic compositions useful for treating and/or preventing Zika virus infection (e.g., in humans) that include one or more Zika virus antigens (e.g., one or more antigens from a whole inactivated Zika virus) from a Zika virus harboring at least one non-human cell adaptation mutation (e.g., a mutation in Zika virus Non-structural protein 1) and/or a Zika virus clonal isolate.

[0012] The present disclosure is based, at least in part, on the surprising finding that both high and low dose vaccines comprising one or more antigens from separately derived clonal virus populations of non-human cell adapted Zika virus were able to induce robust immune responses and provide significant protection from Zika virus infection (See Examples 2 and Example 4 below). Clonal isolation of the Zika virus strains also allowed for: 1) the successful purification of the virus away from contaminating agents (e.g., adventitious agents that may be co-purified with the parental strain), and 2) the production of a genetically homogeneous viral population. Moreover, the present disclosure is based, at least in part, on the finding that clonal isolated Zika viruses harboring an adaptation mutation in protein NS1 grew well and predictably in Vero cells to high titer, and surprisingly, were genetically stable/genetically homogenous without any detectable

mutations in the viral envelope protein (See Examples 1 and 2 below). While a similar mutation in Zika virus Non-structural protein 1 may have been observed in the genomic sequencing analysis of 1 out of 3 published sequences of Zika virus strain PRVABC59 (Yun et al. Genome Announc. 2016 Aug 18;4(4)), this reference fails to teach or suggest that a mutation in NS1 may improve stability of the virus; fails to teach or suggest that a virus harboring the mutation may be used in the development of an effective vaccine against Zika virus; and fails to teach or suggest that such a vaccine may be effective in inducing a robust immune response and providing significant protection from Zika virus infection when used at both low and high doses. Thus, without wishing to be bound by theory, the inventors of the present disclosure have determined that the adaptation mutation in protein NS1 appeared to enhance genetic stability within the Zika virus, resulting in increased/enhanced replication efficiency. Further, the Zika strain harboring an adaptation mutation in protein NS1 was able to be passaged multiple times without developing further mutations. Such a stable Zika virus strain is advantageous as a master virus seed (MVS), or subsequent seeds derived from the MVS, for vaccine production and manufacturing, as the risk of the master virus seed developing undesirable mutations is reduced. Moreover, without wishing to be bound by theory, the adaptation mutation in protein NS1 of the Zika strain of the present disclosure may also reduce or otherwise inhibit the occurrence of undesirable mutations, such as a mutation within the envelope protein E (Env) of the Zika virus strain.

[0013] Accordingly, certain aspects of the present disclosure relate to a vaccine or immunogenic composition containing one or more antigen from a Zika virus, where the Zika virus contains at least one non-human cell adaptation mutation. In some embodiments, the at least one non-human cell adaptation mutation is in Zika virus Non-structural protein 1 (NS1). In some embodiments, the at least one adaptation mutation occurs at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1. In some embodiments, the at least one adaptation mutation is a Trp98Gly mutation.

[0014] Accordingly, certain aspects of the present disclosure relate a vaccine or immunogenic composition comprising a dose of 1µg to 40µg of one antigen from a Zika virus, wherein the Zika virus comprises at least one non-human cell adaptation mutation.

[0015] Accordingly, certain aspects of the present disclosure relate a vaccine or immunogenic composition comprising a dose of 1µg to 40µg of one antigen from a Zika

virus, the Zika virus having a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

[0016] In some embodiments that may be combined with any of the preceding embodiments, the at least one adaptation mutation enhances genetic stability as compared to a Zika virus lacking the at least one adaptation mutation. In some embodiments that may be combined with any of the preceding embodiments, the at least one adaptation mutation enhances viral replication as compared to a Zika virus lacking the at least one adaptation mutation. In some embodiments that may be combined with any of the preceding embodiments, the Zika virus does not comprise a mutation in Envelope protein E (Env).

[0017] In some embodiments that may be combined with any of the preceding embodiments, the non-human cell is a mammalian cell. In some embodiments that may be combined with any of the preceding embodiments, the non-human cell is a monkey cell. In some embodiments, the monkey cell is from a Vero cell line. In some embodiments, the Vero cell line is a WHO Vero 10-87 cell line.

[0018] In some embodiments that may be combined with any of the preceding embodiments, the Zika virus is an African lineage virus or an Asian lineage virus. In some embodiments, the Zika virus is an Asian lineage virus. In some embodiments, the Zika virus is from strain PRVABC59.

[0019] In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition is a purified antigen vaccine or immunogenic composition, a subunit vaccine or immunogenic composition, an inactivated whole virus vaccine or immunogenic composition, or an attenuated virus vaccine or immunogenic composition. In some embodiments, the vaccine or immunogenic composition is an inactivated whole virus vaccine or immunogenic composition. In some embodiments, the vaccine or immunogenic composition comprises a purified inactivated whole Zika virus. In some embodiments, the vaccine or immunogenic composition comprises a purified inactivated whole Zika virus comprising a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1. In some embodiments, the vaccine or immunogenic composition comprises a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1. In some embodiments, the vaccine

or immunogenic composition comprises a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59. In some embodiments, the vaccine or immunogenic composition comprises a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2. In some embodiments, the vaccine or immunogenic composition comprises a purified inactivated whole Zika which differs from strain PRVABC59 in a Trp98Gly mutation at position 98 of SEQ ID NO: 1.

[0020] In some embodiments that may be combined with any of the preceding embodiments, the virus was chemically inactivated. In some embodiments, the virus was chemically inactivated with one or more of a detergent, formalin, beta-propiolactone (BPL), binary ethylamine (BEI), acetyl ethyleneimine, methylene blue, and psoralen. In some embodiments, the virus was chemically inactivated with formalin.

[0021] In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition further contains an adjuvant. In some embodiments, the adjuvant is selected from aluminum salts, toll-like receptor (TLR) agonists, monophosphoryl lipid A (MLA), synthetic lipid A, lipid A mimetics or analogs, MLA derivatives, cytokines, saponins, muramyl dipeptide (MDP) derivatives, CpG oligos, lipopolysaccharide (LPS) of gram-negative bacteria, polyphosphazenes, emulsions, virosomes, cochleates, poly(lactide-co-glycolides) (PLG) microparticles, poloxamer particles, microparticles, liposomes, Complete Freund's Adjuvant (CFA), and/or Incomplete Freund's Adjuvant (IFA). In some embodiments, the adjuvant is an aluminum salt. In some embodiments, the adjuvant is selected from the group consisting of alum, aluminum phosphate, aluminum hydroxide, potassium aluminum sulfate, and Alhydrogel 85. In some embodiments, at least 75%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% of the one or more antigens are adsorbed to the adjuvant.

[0022] In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition is a low or medium dose vaccine or immunogenic composition (e.g., containing from about 1µg to about 5µg antigen or 5µg

or antigen 2µg antigen or 5µg antigen). In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition is a high dose vaccine or immunogenic composition (e.g., containing about 10µg antigen). In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition contains from about 1 µg to about 25 µg of the one or more antigens, in particular 2 µg, 5 µg or 10 µg, or in particular 10 µg of the one or more antigens. In certain such embodiments the antigen is a purified inactivated whole virus, such as a Zika virus with a mutation which is a tryptophan to glycine substitution at position 98 of SEQ ID NO:1 or at a position corresponding to position 98 of SEQ ID NO: 1 as described herein. In some embodiments, the vaccine or immunogenic composition comprises a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59. In some embodiments, the vaccine or immunogenic composition comprises a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2. In certain such embodiments the Zika virus is a plaque purified clonal Zika virus isolate. In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition contains from about 0.1 µg to about 100 µg Zika virus antigen or Env. In some embodiments, the vaccine or immunogenic composition is unadjuvanted. In some embodiments that may be combined with any of the preceding embodiments, the Zika virus is a clonal isolate. In some embodiments, the clonal isolate is substantially free of one or more adventitious agents (e.g., free of one or more adventitious agents that may be co-purified with the parental strain).

[0023] Other aspects of the present disclosure relate to a vaccine comprising a Zika virus having a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1. In some embodiments, the vaccine comprises a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59. In some embodiments, the vaccine comprises a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the

Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2. In certain such embodiments the Zika virus is a plaque purified clonal Zika virus isolate.

[0024] Other aspects of the present disclosure relate to a vaccine or immunogenic composition containing: a) an aluminum salt adjuvant; and b) a purified inactivated whole Zika virus, where the Zika virus contains a non-human cell adaptation mutation, and where the non-human cell adaptation mutation is a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

[0025] Other aspects of the present disclosure relate to a method of treating or preventing, in particular preventing Zika virus infection in a subject in need thereof, including administering to the subject a therapeutically effective amount of any of the vaccines or immunogenic compositions described herein.

[0026] Other aspects of the present disclosure relate to a method for inducing an immune response in a subject in need thereof, including administering to the subject an immunogenic amount of any of the vaccines or immunogenic compositions described herein.

[0027] In one aspect the present disclosure relates to a method of treating or preventing, in particular preventing Zika virus infection in a subject in need thereof, comprising administering to the subject the vaccine or immunogenic composition.

[0028] In one aspect the present disclosure relates to a method for inducing an immune response against a Zika virus antigen in a subject in need thereof, comprising administering to the subject the vaccine or immunogenic composition.

[0029] In one aspect the present disclosure relates to a method of preventing Zika virus disease in a subject in need thereof, comprising administering to the subject the vaccine or immunogenic composition. In this case the disease relates to mild fever, maculopapular rash, conjunctivitis and arthralgia. Furthermore the Zika virus is a neurotropic flavivirus that can potentially cause disease within the central nervous system and Guillain-Barré Syndrome (GBS).

[0030] In one aspect the present disclosure relates to a method of preventing Zika virus disease in a fetus or newborn in need thereof, comprising administering to the pregnant subject or a subject that intends to become pregnant or woman of childbearing potential the vaccine or immunogenic composition. The Zika disease in this case relates to serious outcomes for the fetus and newborn. The spectrum of congenital anomalies associated with Zika virus infection, known as Congenital Zika Syndrome (CZS), consists of severe microcephaly with partially collapsed skull, cerebral cortices with subcortical calcifications, macular scarring and focal pigmentary retinal mottling, congenital contractures, and marked early hypertonia with symptoms of extrapyramidal involvement.

[0031] In one aspect the present disclosure relates to a vaccine or immunogenic composition of for use in a method of treating or preventing, in particular preventing Zika virus infection in a subject in need thereof, in a method for inducing an immune response against a Zika virus antigen in a subject in need thereof, and in a method of preventing Zika virus disease in a subject, fetus or newborn in need thereof.

[0032] In one aspect the present disclosure relates to the use of the vaccine or immunogenic composition in the manufacture of a medicament for a method of treating or preventing, in particular preventing Zika virus infection in a subject in need thereof, a method for inducing an immune response in a subject in need thereof, and for a method of preventing Zika virus disease in a subject fetus or newborn in need thereof.

[0033] Accordingly, certain aspects of the present disclosure relates to a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising a Zika antigen, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 300, or greater than 500, or greater than 1000, or greater than 1500, or greater than 2000, or greater than 3000, as determined by the plaque reduction neutralization test (PRNT).

[0034] Accordingly, certain aspects of the present disclosure relates to a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart, and wherein the administration of the vaccine or immunogenic composition induces 28 days after the boost administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects, which are at least 10 times, or at least 15 times, or at least 20 times, or at least 25 times higher than the geometric mean neutralizing antibodies titers induces 28 days after the prime administration, as determined by the plaque reduction neutralization test (PRNT). The boost administration thus provides for very high geometric mean neutralizing antibodies titers responsible for a long term protection

[0035] Accordingly, certain aspects of the present disclosure relate a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a single dose or prime administration, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 10, or greater than 50, or greater than 100, or greater than 200, or greater than 250, as determined by the plaque reduction neutralization test (PRNT). The high geometric mean neutralizing antibodies titers indicate an early onset of protection which is beneficial in an outbreak situation or a traveler visiting an endemic area within a short period of time from the administration of the vaccine or immunogenic composition.

[0036] Within the meaning of this disclosure PRNT refers to Zika virus Neutralizing antibody titers determined by a plaque reduction neutralization test (PRNT) as described previously (See Sun, W. et al. Protection of Rhesus monkeys against dengue virus challenge after tetravalent live attenuated dengue virus vaccination. J. Infect. Dis. 193,

1658–1665 (2006). Muthumani K, Griffin BD, Agarwal S, et al. In vivo protection against ZIKV infection and pathogenesis through passive antibody transfer and active immunisation with a prMEnv DNA vaccine. NPJ Vaccines 2016; 1: 16021). The Zika strain used for PRNT assay development was PRVABC59.

[0037] Within the meaning of this disclosure seropositivity is defined as titer ≥ 10 as determined by the plaque reduction neutralization test (PRNT); Zika virus seronegative subjects (titer <10) as determined by the plaque reduction neutralization test (PRNT), Seroconversion is defined as: Zika virus seronegative subjects (titer <10) have titer ≥10 post-vaccination as determined by the plaque reduction neutralization test (PRNT); Results < 10 as determined by the plaque reduction neutralization test (PRNT) are assigned a titer of 5; Titers ≥ 10 (limit of detection) and < 26 (lower limit of quantification) as determined by the plaque reduction neutralization test (PRNT) are assigned a value of 13.

[0038] Flavivirus naïve subjects for the present disclosure are defined to be subjects without detectable serum antibodies against a panel of flaviviruses, as measured by a reactive antibody based assay (Luminex). Flavivirus screening assay is based on a luminex platform to simultaneously detect multiple target antigens in the same sample. This bead based assay is sensitive, specific and reproducible. For ZIK101, the antigens targeted are Zika, Dengue, Yellow fever, JEV, USUV, SLEV and WNV. Due to cross reactivity among Flaviviruses, the current antigen set would help detect any prior Flavivirus exposure. References for luminex concept are: Dias D, Van Doren J, Schlottmann S, Kelly S, Puchalski D, Ruiz W, Boerckel P, Kessler J, Antonello JM, Green T, Brown M, Smith J, Chirmule N, Barr E, Jansen KU, Esser MT. 2005. Optimization and validation of a multiplexed Luminex assay to quantify antibodies to neutralizing epitopes on human papillomaviruses 6, 11, 16, and 18. Clin. Diagn. Lab. Immunol. 12:959–969 [PMC free article] [PubMed]. Ayouba A et al Development of a Sensitive and Specific Serological Assay Based on Luminex Technology for Detection of Antibodies to Zaire Ebola Virus. J Clin Microbiol. 2017 Dec 28;55(1):165-176. doi: 10.1128/JCM.01979-16.

[0039] Witin the meaning of this disclosure endemic is defined as areas with risk of infection as defined by the Centers for Disease Control and Prevention, such as for example as of March 2018, namely: Asia: Bangladesh, Burma (Myanmar), Cambodia, India, Indonesia, Laos, Malaysia, Maldives, Pakistan, Philippines, Singapore, Thailand, Timor-

Leste (East Timor), Vietnam.The Pacific Islands: Fiji, Marshall Islands, Papua New Guinea, Samoa, Solomon Islands, Tonga. The Caribbean: Anguilla; Antigua and Barbuda; Aruba; Barbados; Bonaire; British Virgin Islands; Cuba; Curaçao; Dominica; Dominican Republic; Grenada; Haiti; Jamaica; Montserrat; the Commonwealth of Puerto Rico, a US territory; Saba; Saint Kitts and Nevis; Saint Lucia; Saint Martin; Saint Vincent and the Grenadines; Sint Eustatius; Sint Maarten; Trinidad and Tobago; Turks and Caicos Islands; US Virgin Islands. North America: Mexico Central America: Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama South America: Argentina, Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Peru, Suriname, Venezuela Africa: Angola, Benin, Burkina-Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Congo (Congo-Brazzaville), Côte d'Ivoire, Democratic Republic of the Congo (Congo-Kinshasa), Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Mali, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, South Sudan, Sudan, Tanzania, Togo, Uganda. This areas may change.

[0040] Accordingly, certain aspects of the present disclosure relate to a method for inducing an immune response in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising a Zika antigen, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration geometric mean neutralizing antibodies titers in a subject population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 300, or greater than 500, or greater than 1000, or greater than 1500, or greater than 2000, or greater than 3000, or greater than 5000, or greater than 10,000, as determined by the reporter virus particle neutralization assay (RVP).

[0041] Accordingly, certain aspects of the present disclosure relate to a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a single dose or prime administration, and wherein the administration of the vaccine or immunogenic composition

induces 14 and/or 28 days after the single dose or prime administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 300, or greater than 500, greater than 1000, or greater than 2000, as determined by the reporter virus particle neutralization assay (RVP). The high geometric mean neutralizing antibodies titers indicate an early onset of protection which is beneficial in an outbreak situation or a traveler visiting an endemic area within a short period of time from the administration of the vaccine or immunogenic composition.

[0042] Within the meaning of this disclosure Reporter virus particle (RVP) neutralization assay refers to Zika Neutralizing antibody titers were analyzed by titration of serum samples with a constant amount of Zika RVPs in Vero cells grown in 96-well plates. RVPs contained the prME proteins of Zika (strain SPH2012) and a Dengue-based Renilla luciferase reporter. Briefly, sera were heat inactivated at 56°C for 30 min, diluted, and then incubated at 37°C with RVPs. The serum/RVP mixture was then mixed with Vero cells and incubated for 72 hours at 37°C ± 2°C/ 5% CO2 before detection with luciferase substrate. Data was analyzed using JMP11 non-linear 4 parameter analysis, normalized to a positive tracking control and effective dose 50% (EC50) was reported.

[0043] Accordingly, certain aspects of the present disclosure relate a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising a Zika antigen, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of 100% in a population of at least 20 seronegative subjects.

[0044] Accordingly, certain aspects of the present disclosure relate to a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as single dose or prime administration and wherein the administration of the vaccine or immunogenic composition

induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 60%, 70%, 80% or 90% in a population of at least 20 Zika virus seronegative subjects. The high seroconversion rate indicates an early onset of protection, which is beneficial in an outbreak situation or a traveler visiting an endemic area within a short period of time from the administration of the vaccine or immunogenic composition.

[0045] The above methods are to be understood to also relate to corresponding uses of a vaccine or immunogenic composition comprising one antigen from a Zika virus as disclosed herein for the manufacture of a medicament for the treating or preventing Zika virus infection.

[0046] The above methods are to be understood to also relate to a vaccine or immunogenic composition comprising one antigen from a Zika virus as disclosed herein for use the treating or preventing Zika virus infection.

[0047] In some embodiments the administration is intramuscular or subcutaneous. In some embodiments the administration includes the administration of two doses of the vaccine or immunogenic composition as described herein (e.g. 10 µg purified inactivated whole virus, such as a Zika virus with a mutation which is a tryptophan to glycine substitution at position 98 of SEQ ID NO:1 or at a position corresponding to position 98 of SEQ ID NO: 1 as described herein) given about 1 to about 16 weeks apart (first (prime) and a second (boost) administration). In certain such embodiments the Zika virus is a plaque purified clonal Zika virus isolate.

[0048] Other aspects of the present disclosure relate to the vaccines or immunogenic compositions as described herein for use in treating or preventing Zika virus infection in a subject in need thereof, for use in inducing an immune response in a subject in need thereof and for use in preventing Zika virus disease in a subject, fetus or newborn in need thereof. In some embodiments the administration is intramuscular or subcutaneous. In some embodiments the administration includes the administration of two doses of the vaccine or immunogenic composition as described herein (e.g. 10 µg purified inactivated whole virus, such as a Zika virus with a mutation which is a tryptophan to glycine substitution at position 98 of SEQ ID NO:1 or at a position corresponding to position 98 of SEQ ID NO: 1 as described herein) given about 1 to about 16 weeks apart (first (prime) and a second

(boost) administration). In certain such embodiments the Zika virus is a plaque purified clonal Zika virus isolate.

[0049] Other aspects of the present disclosure relate to the use of the vaccines or immunogenic compositions as described herein in the manufacture of a medicament for treating or preventing Zika virus infection in a subject in need thereof for inducing an immune response in a subject in need thereof and in preventing Zika virus disease in a subject, fetus or newborn in need thereof. In some embodiments the administration is intramuscular or subcutaneous. In some embodiments the administration includes the administration of two doses of the vaccine or immunogenic composition as described herein (e.g. 10 μg purified inactivated whole virus, such as a Zika virus with a mutation which is a tryptophan to glycine substitution at position 98 of SEQ ID NO:1 or at a position corresponding to position 98 of SEQ ID NO: 1 as described herein) given about 1 to about 16 weeks apart (first (prime) and a second (boost) administration). In certain such embodiments the Zika virus is a plaque purified clonal Zika virus isolate.

[0050] In some embodiments that may be combined with any of the preceding embodiments, the subject is a human. In some embodiments, the subject is pregnant or intends to become pregnant or woman of childbearing potential.

[0051] In some embodiments that may be combined with any of the preceding embodiments, administration of the vaccine or immunogenic composition induces a protective immune response in the subject. In some embodiments, the protective immune response induced in the subject is greater than a protective immune response induced in a corresponding subject administered a vaccine or immunogenic composition containing one or more antigens from a Zika virus lacking the at least one non-human cell adaptation mutation. In some embodiments that may be combined with any of the preceding embodiments, administration of the vaccine or immunogenic composition induces the generation of neutralizing antibodies to Zika virus in the subject. In some embodiments, the concentration of neutralizing antibodies generated in the subject is higher than a concentration of neutralizing antibodies generated in a corresponding subject administered a vaccine or immunogenic composition comprising one or more antigens from a Zika virus lacking the at least one non-human cell adaptation mutation.

[0052] In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition is administered by a route selected from subcutaneous administration, transcutaneous administration, intradermal administration, subdermal administration, intramuscular administration, peroral administration, intranasal administration, buccal administration, intraperitoneal administration, intravaginal administration, anal administration and/or intracranial administration. In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition is administered one or more times. In some embodiments, the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration. In some embodiments, the second (boost) administration is administered at least 28 days after the first (prime) administration. In some embodiments the administration includes the administration of two doses of the vaccine or immunogenic composition as described herein (e.g. 10 μg purified inactivated whole virus, such as a Zika virus with a mutation which is a tryptophan to glycine substitution at position 98 of SEQ ID NO:1 or at a position corresponding to position 98 of SEQ ID NO: 1 as described herein) given about 1 to about 16 weeks apart (first (prime) and a second (boost) administration). In certain such embodiments the Zika virus is a plaque purified clonal Zika virus isolate.

[0053] In some embodiments that may be combined with any of the preceding embodiments, the virus preparation is mixed with an adjuvant. In some embodiments, the adjuvant is selected from aluminum salts, toll-like receptor (TLR) agonists, monophosphoryl lipid A (MLA), synthetic lipid A, lipid A mimetics or analogs, MLA derivatives, cytokines, saponins, muramyl dipeptide (MDP) derivatives, CpG oligos, lipopolysaccharide (LPS) of gram-negative bacteria, polyphosphazenes, emulsions, virosomes, cochleates, poly(lactide-co-glycolides) (PLG) microparticles, poloxamer particles, microparticles, liposomes, Complete Freund's Adjuvant (CFA), and/or Incomplete Freund's Adjuvant (IFA). In some embodiments, the adjuvant is an aluminum salt. In some embodiments, the adjuvant is selected from alum, aluminum phosphate, aluminum hydroxide, potassium aluminum sulfate, and/or Alhydrogel 85. In some embodiments, at least 75%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% of one or more antigens in the virus preparation are adsorbed to the adjuvant.

[0054] In some embodiments that may be combined with any of the preceding embodiments, the at least one non-human cell adaptation mutation is in Zika virus NS1. In some embodiments, the at least one adaptation mutation occurs at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1. In some embodiments, the at least one adaptation mutation is a Trp98Gly mutation. In some embodiments that may be combined with any of the preceding embodiments, the at least one adaptation mutation enhances genetic stability as compared to a Zika virus lacking the at least one adaptation mutation. In some embodiments that may be combined with any of the preceding embodiments, the at least one adaptation mutation enhances viral replication as compared to a Zika virus lacking the at least one adaptation mutation. In some embodiments that may be combined with any of the preceding embodiments, the Zika virus does not comprise a mutation in Envelope protein E (Env).

[0055] In some embodiments that may be combined with any of the preceding embodiments, the population of Zika viruses is heterogeneous. In some embodiments that may be combined with any of the preceding embodiments, the population of Zika viruses comprises a Zika virus clinical isolate. In some embodiments, the Zika virus clinical isolate is from strain PRVABC59. In some embodiments that may be combined with any of the preceding embodiments, the population of Zika viruses comprises a Zika virus that has been previously passaged one or more times in cell culture. In some embodiments that may be combined with any of the preceding embodiments, the inoculum comprises human serum. In some embodiments that may be combined with any of the preceding embodiments, the inoculum comprises one or more adventitious agents. In some embodiments, the Zika virus clonal isolate is substantially free of the one or more adventitious agents.

[0056] In some embodiments that may be combined with any of the preceding embodiments, the methods further include one or more additional plaque purifications of the Zika virus clonal isolate. In some embodiments, the Zika virus clonal isolate is further plaque purified two or more times. In some embodiments that may be combined with any of the preceding embodiments, the methods further include passaging the Zika virus clonal isolate one or more times in cell culture. In some embodiments, the Zika virus clonal isolate is passaged two or more times.

[0057] In some embodiments that may be combined with any of the preceding embodiments, the methods further include formulating a vaccine or immunogenic

composition comprising one or more antigens from the Zika virus clonal isolate. In some embodiments, the vaccine or immunogenic composition is a purified antigen vaccine or immunogenic composition, a subunit vaccine or immunogenic composition, an inactivated whole virus vaccine or immunogenic composition, or an attenuated virus vaccine or immunogenic composition. In some embodiments, the vaccine or immunogenic composition is a purified inactivated whole virus vaccine or immunogenic composition. In some embodiments, the Zika virus clonal isolate was chemically inactivated. In some embodiments, the Zika virus clonal isolate was chemically inactivated with one or more of a detergent, formalin, beta-propiolactone (BPL), binary ethylamine (BEI), acetyl ethyleneimine, methylene blue, and psoralen. In some embodiments, the Zika virus clonal isolate was chemically inactivated with formalin.

[0058] In some embodiments that may be combined with any of the preceding embodiments, the methods further include admixing the vaccine or immunogenic composition with an adjuvant. In some embodiments, the adjuvant is selected from aluminum salts, toll-like receptor (TLR) agonists, monophosphoryl lipid A (MLA), synthetic lipid A, lipid A mimetics or analogs, MLA derivatives, cytokines, saponins, muramyl dipeptide (MDP) derivatives, CpG oligos, lipopolysaccharide (LPS) of gram-negative bacteria, polyphosphazenes, emulsions, virosomes, cochleates, poly(lactide-co-glycolides) (PLG) microparticles, poloxamer particles, microparticles, liposomes, Complete Freund's Adjuvant (CFA), and Incomplete Freund's Adjuvant (IFA). In some embodiments, the adjuvant is an aluminum salt. In some embodiments, the adjuvant is selected from alum, aluminum phosphate, aluminum hydroxide, potassium aluminum sulfate, and Alhydrogel 85. In some embodiments, at least 75%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% of the one or more antigens are adsorbed to the adjuvant. In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition comprises 1 µg to about 40 µg of the purified inactivated whole virus, or 1 µg to about 30 µg of the purified inactivated whole virus, or 1 µg to about 20 µg of the purified inactivated whole virus, in particular 2 µg, or 5 µg, or 10 µg, or 15 µg or 20 µg or in particular 10 µg purified inactivated whole virus , such as a Zika virus with a mutation which is a tryptophan to glycine substitution at position 98 of SEQ ID NO:1 or at a position corresponding to position 98 of SEQ ID NO: 1 as described herein. In some embodiments, the vaccine or immunogenic composition comprises 1 µg to about 30 µg of the purified inactivated whole

virus, in particular 2 µg, 5 µg or 10 µg, or in particular 10 µg of a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59. In some embodiments, the vaccine or immunogenic composition comprises 1 µg to about 30 µg of the purified inactivated whole virus, in particular 2 µg, 5 µg or 10 µg, or in particular 10 µg of a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2.

[0059] In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition comprises from about 0.1 µg Env to about 100 µg Env. In certain such embodiments the Zika virus is a plaque purified clonal Zika virus isolate .In some embodiments, the vaccine or immunogenic composition is unadjuvanted.

[0060] In some embodiments that may be combined with any of the preceding embodiments, the Zika virus clonal isolate is a homogenous genetic population. In some embodiments, the Zika virus clonal isolate does not contain a mutation in Envelope protein E (Env). In some embodiments, the Zika virus clonal isolate contains at least one mutation. In some embodiments, the at least one mutation is in Zika virus Non-structural protein 1 (NS1). In some embodiments, the at least one mutation occurs at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1. In some embodiments, the at least one mutation is a Trp98Gly mutation. In some embodiments the at least one mutation is not in Envelope protein E (Env). In some embodiments, the at least one mutation enhances genetic stability as compared to a Zika virus lacking the at least one mutation. In some embodiments, the at least one mutation enhances viral replication as compared to a Zika virus lacking the at least one mutation.

[0061] Other aspects of the present disclosure relate to a vaccine or immunogenic composition containing one or more antigens from a plaque purified clonal Zika virus isolate. In some embodiments, the plaque purified clonal Zika virus isolate was plaque purified from cells contacted with an inoculum comprising a population of Zika viruses. In some embodiments, the cells are non-human cells. In some embodiments, the cells are insect cells. In some embodiments, the insect cells are mosquito cells. In some

embodiments, the cells are mammalian cells. In some embodiments, the mammalian cells are monkey cells. In some embodiments, the monkey cells are from a Vero cell line. In some embodiments, the Vero cell line is a WHO Vero 10-87 cell line.

[0062] In some embodiments that may be combined with any of the preceding embodiments, the population of Zika viruses was heterogeneous. In some embodiments that may be combined with any of the preceding embodiments, the population of Zika viruses comprised a Zika virus clinical isolate. In some embodiments, the Zika virus clinical isolate is from strain PRVABC59. In some embodiments that may be combined with any of the preceding embodiments, the population of Zika viruses comprised a Zika virus that had been previously passaged one or more times in cell culture. In some embodiments that may be combined with any of the preceding embodiments, the inoculum comprised human serum. In some embodiments that may be combined with any of the preceding embodiments, the inoculum comprised one or more adventitious agents. In some embodiments, the plaque purified clonal Zika virus isolate is substantially free of the one or more adventitious agents.

[0063] In some embodiments that may be combined with any of the preceding embodiments, the plaque purified clonal Zika virus isolate is modified as compared to a wild-type Zika virus. In some embodiments that may be combined with any of the preceding embodiments, the plaque purified clonal Zika virus isolate is a homogenous genetic population. In some embodiments that may be combined with any of the preceding embodiments, the plaque purified clonal Zika virus isolate does not include a mutation in Envelope protein E (Env). In some embodiments that may be combined with any of the preceding embodiments, the plaque purified clonal Zika virus isolate comprises at least one mutation. In some embodiments, the at least one mutation is in Zika virus Non-structural protein 1 (NS1). In some embodiments, the at least one mutation occurs at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1. In some embodiments, the at least one mutation is a Trp98Gly mutation. In some embodiments, the at least one mutation is not in Zika virus Envelope protein E (Env). In some embodiments, the at least one mutation enhances genetic stability as compared to a Zika virus lacking the at least one mutation. In some embodiments, the at least one mutation enhances viral replication as compared to a Zika virus lacking the at least one mutation. In some embodiments that may be combined with any of the preceding embodiments, the plaque

purified clonal Zika virus isolate is an African lineage virus or an Asian lineage virus. In some embodiments, the plaque purified clonal Zika virus isolate is an Asian lineage virus.

[0064] In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition is a purified antigen vaccine or immunogenic composition, a subunit vaccine or immunogenic composition, an inactivated whole virus vaccine or immunogenic composition, or an attenuated virus vaccine or immunogenic composition. In some embodiments, the vaccine or immunogenic composition is an inactivated whole virus vaccine or immunogenic composition. In some embodiments that may be combined with any of the preceding embodiments, the plaque purified clonal Zika virus isolate was chemically inactivated. In some embodiments, the plaque purified Zika virus was chemically inactivated with one or more of a detergent, formalin, beta-propiolactone (BPL), binary ethylamine (BEI), acetyl ethyleneimine, methylene blue, and psoralen. In some embodiments, the plaque purified clonal Zika virus isolate was chemically inactivated with formalin.

[0065] In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition further comprises an adjuvant. In some embodiments, the adjuvant is selected from aluminum salts, toll-like receptor (TLR) agonists, monophosphoryl lipid A (MLA), synthetic lipid A, lipid A mimetics or analogs, MLA derivatives, cytokines, saponins, muramyl dipeptide (MDP) derivatives, CpG oligos, lipopolysaccharide (LPS) of gram-negative bacteria, polyphosphazenes, emulsions, virosomes, cochleates, poly(lactide-co-glycolides) (PLG) microparticles, poloxamer particles, microparticles, liposomes, Complete Freund's Adjuvant (CFA), and Incomplete Freund's Adjuvant (IFA). In some embodiments, the adjuvant is an aluminum salt. In some embodiments, the adjuvant is selected from alum, aluminum phosphate, aluminum hydroxide, potassium aluminum sulfate, and Alhydrogel 85. In some embodiments, at least 75%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% of the one or more antigens are adsorbed to the adjuvant. In some embodiments that may be combined with any of the preceding embodiments, the vaccine or immunogenic composition contains from 0.1 µg to about 25 µg of the purified inactivated whole virus, such as a Zika virus with a mutation which is a tryptophan to glycine substitution at position 98 of SEQ ID NO:1 as described herein, in particular 2 µg, 5 µg or 10 µg, or in particular 10 µg purified inactivated whole virus or about 0.1 µg Env to about

100 µg Env. In certain such embodiments the Zika virus is a plaque purified clonal Zika virus isolate. In some embodiments, the vaccine or immunogenic composition is unadjuvanted.

[0066] It is to be understood that one, some, or all of the properties of the various embodiments described above and herein may be combined to form other embodiments of the present disclosure. These and other aspects of the present disclosure will become apparent to one of skill in the art. These and other embodiments of the present disclosure are further described by the detailed description that follows.

Brief description of The drawings

[0067] FIG. 1 shows bright field microscopy images of Vero cell monolayers mock infected (top) or infected with ZIKAV strain PRVABC59 (bottom).

[0068] FIG. 2 shows growth kinetics of ZIKAV PRVABC59 P1 on Vero cell monolayers, as determined by TCID50.

[0069] FIG. 3 shows potency assay testing (TCID50) of Zika virus PRVABC59 P5 clones a-f.

[0070] FIG. 4 shows bright-field microscopy images depicting the cytopathic effect (CPE) of growth of Zika virus PRVABC59 P6 clones a-f on Vero cell monolayers.

[0071] FIG. 5 shows potency assay testing (TCID50) of Zika virus PRVABC59 P6 clones a-f

[0072] FIG. 6 shows an amino acid sequence alignment comparing the envelope glycoprotein sequence of Zika virus near residue 330 from Zika virus strains PRVABC59 P6e (SEQ ID NO: 8) and PRVABC59 (SEQ ID NO: 9) with several other flaviviruses (WNV (SEQ ID NO: 10); JEV (SEQ ID NO: 11); SLEV (SEQ ID NO: 12); YFV (SEQ ID NO: 13); DENV 1 16007 (SEQ ID NO: 14); DENV 2 16681 (SEQ ID NO: 15); DENV 3 16562 (SEQ IDNO: 16); and DENV 4 1036 (SEQ ID NO: 17)).

[0073] FIG. 7 shows an amino acid sequence alignment comparing the NS1 protein sequence of Zika virus near residue 98 from Zika virus strains PRVABC59 P6e (SEQ ID NO: 18) and PRVABC59 (SEQ ID NO: 19) with several other flaviviruses (WNV (SEQ ID

NO: 20); JEV (SEQ ID NO: 21); SLEV (SEQ ID NO: 22); YFV (SEQ ID NO: 23); DENV 1 16007 (SEQ ID NO: 24); DENV 2 16681 (SEQ ID NO: 25); DENV 3 16562 (SEQ IDNO: 26); and DENV 4 1036 (SEQ ID NO: 27)).

[0074] FIG. 8 shows the plaque phenotype of ZIKAV PRVABC59 P6 virus clones a-f compared to ZIKAV PRVABC59 P1 virus.

[0075] FIG. 9 shows the mean plaque size of ZIKAV PRVABC59 P6 virus clones compared to ZIKAV PRVABC59 P1 virus.

[0076] FIG. 10 shows the growth kinetics of ZIKAV PRVABC59 P6 clones a-f in Vero cells under serum-free growth conditions.

[0077] FIG. 11 shows a schematic of the steps taken to prepare PRVABC59 P6b and P6e formulated drug product for the immunization experiments.

[0078] FIG. 12A shows the schedule of dosing of CD-1 mice with vaccine formulations derived from the ZIKAV PRVABC59 P6b and P6e clones. PBS was used as placebo.

[0079] FIG. 12B shows the serum ZIKAV neutralizing antibody titers of CD-1 mice immunized as described in FIG. 12A using vaccine formulations derived from ZIKAV PRVABC59 P6b and P6e clones. ZIKAV neutralizing antibody titers were determined by Reporter Virus Particle (RVP) neutralization assay. Solid lines represent the geometric mean of a group. The limit of detection (1.93 log10) is represented by a dashed line.

[0080] FIG. 13A shows the schedule of dosing of AG129 mice with vaccine formulations derived from the ZIKAV PRVABC59 P6b and P6e clones. PBS was used as a placebo.

[0081] FIG. 13B shows the serum ZIKAV neutralizing antibody titers of AG129 mice immunized as described in FIG. 13A using vaccine formulations derived from ZIKAV PRVABC59 P6b and P6e clones. Solid lines represent the geometric mean of a group. The limit of detection (1.30 log10) is represented by a dashed line. Animals with no detectable titer (<1.30) were assigned a titer of 0.5.

[0082] FIG. 14 shows the mean weight of AG129 test groups post-challenge, represented as a percentage of starting weight. Error bars represent standard deviation.

[0083] FIG. 15 shows the serum viremia of individual AG129 mice two days post-challenge, reported as PFU/mL. Solid lines represent the mean of a group. The limit of detection (2.0 log10) is represented by a dashed line.

[0084] FIG. 16 shows the survival analysis of AG129 test groups post-challenge.

[0085] FIG. 17 shows the pre-challenge serum circulating ZIKAV neutralizing antibody (Nab) titers following passive transfer of pooled sera from vaccinated and challenged AG129 mice.

[0086] FIG. 18 shows the mean body weight of passive transfer and control mice challenged with Zika virus.

[0087] FIG. 19 shows the serum viremia of individual AG129 mice three days post-challenge, reported as PFU/mL.

[0088] FIG. 20 shows the survival analysis of passive transfer and control mice challenged with Zika virus.

[0089] FIG. 21 shows the correlation between ZIKAV neutralizing antibody titers and viremia observed in passive transfer mice.

[0090] FIG. 22 shows the survival analysis of AG129 mice after challenge with preMVS stocks of P6a and P6e using a Kaplan Meier survival curve.

[0091] FIG. 23 shows the mean body weight as expressed in percentage of starting weight at time of invention after challenge with preMVS stocks of P6a and P6e. The dashed line represents 100% of starting weight for reference.

[0092] FIG. 24 shows the serum viremia of individual AG129 mice three days post-challenge with preMVS stocks of P6a and P6e, reported as PFU/mL. The dashed line represents the limit of detection of the assay.

[0093] FIG. 25 shows a summary of the Clinical Study Design for Example 4.

[0094] FIG. 26 shows the Geometric Mean Titers (GMTs) determined using PRNT of the Subjects in Example 4

[0095] FIG. 27 shows the percentage of subjects achieving seroconversion determined using PRNT at Day 29 (day 28 after prime dose) and Day 57 (28 days after boost dose) of the study described in Example 4.

[0096] FIG. 28 shows the plot of the percentage of subjects achieving a particular Geometric Mean Titer (determined using PRNT) on day 29 (day 28 after prime dose) of the study described in Example 4.

[0097] FIG. 29 shows the plot of the percentage of subjects achieving a particular Geometric Mean Titer (determined using PRNT) on day 57 (day 56 after prime dose) of the study described in Example 4.

DETAILED DESCRIPTION

General Techniques

[0098] The techniques and procedures described or referenced herein are generally well understood and commonly employed using conventional methodology by those skilled in the art, such as, for example, the widely utilized methodologies described in Sambrook et al., *Molecular Cloning: A Laboratory Manual* 3d edition (2001) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; *Current Protocols in Molecular Biology* (F.M. Ausubel, et al. eds., (2003)); the series *Methods in Enzymology* (Academic Press, Inc.): *PCR 2: A Practical Approach* (M.J. MacPherson, B.D. Hames and G.R. Taylor eds. (1995)), *Antibodies, A Laboratory Manual (*Harlow and Lane, eds. (1988), and *Animal Cell Culture* (R.I. Freshney, ed. (1987)); *Oligonucleotide Synthesis* (M.J. Gait, ed., 1984); *Methods in Molecular Biology* (J. M. Walker, ed. Humana Press (1983)); *Cell Biology: A Laboratory Notebook* (J.E. Celis, ed., Academic Press (1998)) Academic Press; *Animal Cell Culture* (R.I. Freshney), ed., 1987); *Introduction to Cell and Tissue Culture* (J.P. Mather and P.E. Roberts, eds. Plenum Press (1998)); *Cell and Tissue Culture: Laboratory Procedures* (A. Doyle, J.B. Griffiths, and D.G. Newell, eds., J. Wiley and Sons (1993-8)); *Handbook of Experimental Immunology* (D.M. Weir and C.C. Blackwell, eds.); *Gene Transfer Vectors for Mammalian Cells* (J.M. Miller and M.P. Calos, eds., Cold Spring Harbor Laboratory (1987)); *PCR: The Polymerase Chain Reaction*, (Mullis et al., eds., Springer (1994)); *Current Protocols in Immunology* (J.E. Coligan et al., eds., Wiley (1991)); *Short Protocols in Molecular Biology* (Wiley and Sons, 1999); *Immunobiology* (C.A. Janeway and P. Travers, (1997)); *Antibodies* (P. Finch, 1997); *Antibodies: A*

Practical Approach (D. Catty., ed., IRL Press, (1988-1989)); *Monoclonal Antibodies: A Practical Approach* (P. Shepherd and C. Dean, eds., Oxford University Press, (2000)); *Using Antibodies: A Laboratory Manual* (E. Harlow and D. Lane (Cold Spring Harbor Laboratory Press, (1999)); and *The Antibodies* (M. Zanetti and J. D. Capra, eds., Harwood Academic Publishers, (1995)).

Zika virus

[0099] Certain aspects of the present disclosure relate to at least one Zika virus (e.g., a Zika virus clonal isolate, a Zika virus purified by the methods described herein, a Zika virus comprising one or more non-human cell adaptation mutations, etc.) that may be useful in vaccines and/or immunogenic compositions including, without limitation, purified viruses, inactivated viruses, attenuated viruses, recombinant viruses, or purified and/or recombinant viral proteins for subunit vaccines.

[00100] Zika virus (ZIKV) is a mosquito-borne flavivirus first isolated from a sentinel rhesus monkey in the Zika Forest in Uganda in 1947. Since that time, isolations have been made from humans in both Africa and Asia, and more recently, the Americas. ZIKV is found in two (possibly three) lineages: an African lineage (possibly separate East and West African lineages) and an Asian lineage. Accordingly, examples of suitable Zika viruses of the present disclosure include, without limitation, viruses from the African and/or Asian lineages. In some embodiments, the Zika virus is an African lineage virus. In some embodiments, the Zika virus is an Asian lineage virus. Additionally, multiple strains within the African and Asian lineages of Zika virus have been previously identified. Any one or more suitable strains of Zika virus known in the art may be used in the present disclosure, including, for examples, strains Mr 766, ArD 41519, IbH 30656, P6-740, EC Yap, FSS13025, ArD 7117, ArD 9957, ArD 30101, ArD 30156, ArD 30332, HD 78788, ArD 127707, ArD 127710, ArD 127984, ArD 127988, ArD 127994, ArD 128000, ArD 132912, 132915, ArD 141170, ArD 142623, ArD 149917, ArD 149810, ArD 149938, ArD 157995, ArD 158084, ArD 165522, ArD 165531, ArA 1465, ArA 27101, ArA 27290, ArA 27106, ArA 27096, ArA 27407, ArA 27433, ArA 506/96, ArA 975-99, Ara 982-99, ArA 986-99, ArA 2718, ArB 1362, Nigeria68, Malaysia66, Kedougou84, Suriname, MR1429, PRVABC59, ECMN2007, DakAr41524, H/PF/2013, R103451, 103344, 8375, JMB-185, ZIKV/H, sapiens/Brazil/Natal/2015, SPH2015, ZIKV/Hu/Chiba/S36/2016, and/or Cuba2017. In some embodiments, strain PRVABC59 is used in the present disclosure.

[00101] In some embodiments, an example of a Zika virus genome sequence is set forth below as SEQ ID NO: 2:

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    1 gttgttgatc tgtgtgaatc agactgcgac agttcgagtt tgaagcgaaa
gctagcaaca

   61 gtatcaacag gttttatttt ggatttggaa acgagagttt ctggtcatga aaaacccaaa
  121 aaagaaatcc ggaggattcc ggattgtcaa tatgctaaaa cgcggagtag cccgtgtgag
  181 ccccctttggg ggcttgaaga ggctgccagc cggacttctg ctgggtcatg ggcccatcag
  241 gatggtcttg gcgattctag ccttttttgag attcacggca atcaagccat cactgggtct
  301 catcaataga tggggttcag tggggaaaaa agaggctatg gaaacaataa agaagttcaa
  361 gaaagatctg gctgccatgc tgagaataat caatgctagg aaggagaaga agagacgagg
  421 cgcagatact agtgtcggaa ttgttggcct cctgctgacc acagctatgg cagcggaggt
  481 cactagacgt gggagtgcat actatatgta cttggacaga aacgatgctg gggaggccat
  541 atcttttcca accacattgg ggatgaataa gtgttatata cagatcatgg atcttggaca
  601 catgtgtgat gccaccatga gctatgaatg ccctatgctg gatgaggggg tggaaccaga
  661 tgacgtcgat tgttggtgca acacgacgtc aacttgggtt gtgtacggaa cctgccatca
  721 caaaaaaggt gaagcacgga gatctagaag agctgtgacg ctccccctccc attccaccag
  781 gaagctgcaa acgcggtcgc aaacctggtt ggaatcaaga gaatacacaa agcacttgat
  841 tagagtcgaa aattggatat tcaggaaccc tggcttcgcg ttagcagcag ctgccatcgc
  901 ttggcttttg ggaagctcaa cgagccaaaa agtcatatac ttggtcatga tactgctgat
  961 tgccccggca tacagcatca ggtgcatagg agtcagcaat agggactttg tggaaggtat
 1021 gtcaggtggg acttgggttg atgttgtctt ggaacatgga ggttgtgtca ccgtaatggc
 1081 acaggacaaa ccgactgtcg acatagagct ggttacaaca acagtcagca acatggcgga
 1141 ggtaagatcc tactgctatg aggcatcaat atcagacatg gcttctgaca gccgctgccc
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 1261 gttagtggac agaggctggg gaaatggatg tggacttttt ggcaaaggga gcctggtgac
 1321 atgcgctaag tttgcatgct ccaagaaaat gaccgggaag agcatccagc cagagaatct
 1381 ggagtaccgg ataatgctgt cagttcatgg ctcccagcac agtgggatga tcgttaatga
 1441 cacaggacat gaaactgatg agaatagagc gaaagttgag ataacgccca attcaccgag
 1501 agccgaagcc accctggggg gttttggaag cctaggactt gattgtgaac cgaggacagg
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 1741 cgtggttcta gggagtcaag aaggagcagt tcacacggcc cttgctggag ctctggaggc
 1801 tgagatggat ggtgcaaagg gaaggctgtc ctctggccac ttgaaatgtc gcctgaaaat
 1861 ggataaactt agattgaagg gcgtgtcata ctccttgtgt actgcagcgt tcacattcac
 1921 caagatcccg gctgaaacac tgcacgggac agtcacagtg gaggtacagt acgcagggac
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 2281 aggcgctctc aactcattgg gcaagggcat ccatcaaatt tttggagcag ctttcaaatc
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[00102] In some embodiments, the Zika virus may comprise the genome sequence of GenBank Accession number KU501215.1. In some embodiments, the Zika virus is from strain PRVABC59. In some embodiments the genome sequence of GenBank Accession number KU501215.1 comprises the sequence of SEQ ID NO: 2. In some embodiments, the Zika virus may comprise a genomic sequence that has at least 70%, at least 71%, at least 72%, at least 73%, at least 74%,at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%,at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity with the sequence of SEQ ID NO: 2.

[00103] In some embodiments, the Zika virus may comprise at least one polypeptide encoded by the sequence of SEQ ID NO: 2. In some embodiments, the Zika virus may comprise at least one polypeptide having an amino acid sequence that has at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity with an amino acid sequence encoded by the sequence of SEQ ID NO: 2.

[00104] Accordingly, in some embodiments, Zika viruses of the present disclosure may be used in any of the vaccines and/or immunogenic compositions disclosed herein. For example, Zika viruses of the present disclosure may be used to provide one or more antigens useful for treating or preventing Zika virus infection in a subject in need thereof and/or for inducing an immune response, such as a protective immune response, against Zika virus in a subject in need thereof.

Viral Antigens

[00105] In some embodiments, the present disclosure relates to one or more antigens from any Zika virus described herein useful in vaccines and/or immunogenic compositions including, without limitation, purified viruses, inactivated viruses, attenuated viruses, recombinant viruses, or purified and/or recombinant viral proteins for subunit vaccines. In some embodiments, the vaccines and/or immunogenic compositions include inactivated whole viruses.

[00106] Antigens of the present disclosure may be any substance capable of eliciting an immune response. Examples of suitable antigens include, but are not limited to, whole virus, attenuated virus, inactivated virus, proteins, polypeptides (including active proteins and individual polypeptide epitopes within proteins), glycopolypeptides, lipopolypeptides, peptides, polysaccharides, polysaccharide conjugates, peptide and non-peptide mimics of polysaccharides and other molecules, small molecules, lipids, glycolipids, and carbohydrates.

[00107] Antigens of the present disclosure may be from any Zika virus (e.g., a Zika virus clonal isolate) produced from one or more cells in cell culture (e.g., via plaque purification). Any suitable cells known in the art for producing Zika virus may be used, including, for example, insect cells (e.g., mosquito cells such as CCL-125 cells, Aag-2 cells, RML-12 cells, C6/36 cells, C7-10 cells, AP-61 cells, A.t. GRIP-1 cells, A.t. GRIP-2 cells, A.t. GRIP-3 cells, UM-AVE1 cells, Mos.55 cells, Sua1B cells, 4a-3B cells, Mos.42 cells, MSQ43 cells, LSB-AA695BB cells, NIID-CTR cells, TRA-171, cells, and additional cells or cell lines from mosquito species such as Aedes aegypti, Aedes albopictus, Aedes pseudoscutellaris, Aedes triseriatus, Aedes vexans, Anopheles gambiae, Anopheles stephensi, Anopheles albimus, Culex quinquefasciatus, Culex theileri, Culex tritaeniorhynchus, Culex bitaeniorhynchus, and/or Toxorhynchites amboinensis), and mammalian cells (e.g., VERO cells (from monkey kidneys), LLC-MK2 cells (from monkey kidneys), MDBK cells, MDCK cells, ATCC CCL34 MDCK (NBL2) cells, MDCK 33016 (deposit number DSM ACC 2219 as described in WO97/37001) cells, BHK21-F cells, HKCC cells, or Chinese hamster ovary cells (CHO cells). In some embodiments, antigens of the present disclosure are from a Zika virus (e.g., a Zika virus clonal isolate) produced from a non-human cell (e.g., via plaque purification). In some embodiments, antigens of the present disclosure are from a Zika virus (e.g., a Zika virus clonal isolate) produced from an

insect cell (e.g., via plaque purification). In some embodiments, antigens of the present disclosure are from a Zika virus (e.g., a Zika virus clonal isolate) produced from a mosquito cell (e.g., via plaque purification). In some embodiments, antigens of the present disclosure are from a Zika virus (e.g., a Zika virus clonal isolate) produced from a mammalian cell (e.g., via plaque purification). In some embodiments, antigens of the present disclosure are from a Zika virus (e.g., a Zika virus clonal isolate) produced from a VERO cell (e.g., via plaque purification). Methods of purifying a virus by performing plaque purification are known to one of ordinary skill in the art (See e.g., Example 1 below).

[00108] Antigens of the present disclosure may include at least one non-human cell adaptation mutation. Adaptation mutations may be generated by adapting a virus to growth in a particular cell line. For example, a cell may be transfected or electroporated with a virus, RNA transcribed from a virus (e.g., an infectious virus, or infectious clone), and/or RNA purified from a whole virus and passaged such that the virus and/or viral RNA replicates and its nucleic acid mutates. Nucleic acid mutations may be point mutations, insertion mutations, or deletion mutations. Nucleic acid mutations may lead to amino acid changes within viral proteins that facilitate growth of the virus in a non-human cell. Adaptation mutations may facilitate phenotypic changes in the virus, including altered plaque size, growth kinetics, temperature sensitivity, drug resistance, virulence, and virus yield in cell culture. These adaptive mutations may be useful in vaccine manufacture by increasing the speed, yield, and consistency of virus cultured in a cell line. Adaptive mutations may change (e.g., enhance or decrease) immunogenicity of viral antigens by altering the structure of immunogenic epitopes. In addition, adaptive mutations may also increase the genetic stability of the virus and/or reduce or otherwise inhibit the development of undesirable mutations in the virus through multiple (e.g., at least five, at least six, at least seven, at least eight, at least nine, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or more) passages.

[00109] Accordingly, in certain embodiments, antigens of the present disclosure include at least one non-human cell adaptation mutation. In certain embodiments, the adaptation mutation is a mutation of a viral antigen to a non-human cell. In some embodiments, the non-human cell is a mammalian cell. Any suitable mammalian cell known in the art may be used, including, without limitation, VERO cells (from monkey kidneys), LLC-MK2 cells (from monkey kidneys), MDBK cells, MDCK cells, ATCC

CCL34 MDCK (NBL2) cells, MDCK 33016 (deposit number DSM ACC 2219 as described in WO97/37001) cells, BHK21-F cells, HKCC cells, or Chinese hamster ovary cells (CHO cells). In some embodiments, the non-human cell is a monkey cell. In some embodiments, the monkey cell is from a Vero cell line. Any suitable Vero cell line known in the art may be used, including, without limitation, WHO Vero 10-87, ATCC CCL-81, Vero 76 (ATCC Accession No. CRL-1587), or Vero C1008 (ATCC Accession No. CRL-1586). In some embodiments, the Vero cell line is WHO Vero 10-87.

[00110] Zika viruses possess a positive sense, single-stranded RNA genome encoding both structural and nonstructural polypeptides. The genome also contains non-coding sequences at both the 5'- and 3'- terminal regions that play a role in virus replication. Structural polypeptides encoded by these viruses include, without limitation, capsid (C), precursor membrane (prM), and envelope (E). Non-structural (NS) polypeptides encoded by these viruses include, without limitation, NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5.

[00111] In certain embodiments, antigens of the present disclosure may contain at least one (e.g., at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, etc.) non-human cell adaptation mutations within one or more (e.g., one or more, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or all ten) viral antigens/polypeptides, including, without limitation, C, prM, E, NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. In some embodiments, antigens of the present disclosure include at least one non-human cell adaptation mutation in Zika virus Non-structural protein 1 (NS1). In some embodiments, antigens of the present disclosure include whole, inactivated virus that may contain at least one (e.g., at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least 10, etc.) non-human cell adaptation mutations. In some embodiments, antigens of the present disclosure include whole, inactivated virus that may contain at least one non-human cell adaptation mutation in Zika virus Non-structural protein 1 (NS1).

[00112] In some embodiments, the at least one non-human cell adaptation mutation is within the NS1 polypeptide. The amino acid sequence of a wild-type, non-cell adapted NS1 polypeptide from an exemplary Zika virus strain is set forth as:

[00113] DVGCSVDFSKKETRCGTGVFVYNDVEAWRDRYKYHPDSPRRLAAA VKQAWEDGICGISSVSRMENIMWRSVEGELNAILEENGVQLTVVVGSVKNPMWR GPQRLPVPVNELPHGWKAWGKSYFVRAAKTNNSFVVDGDTLKECPLKHRAWNSF LVEDHGFGVFHTSVWLKVREDYSLECDPAVIGTAVKGKEAVHSDLGYWIESEKND TWRLKRAHLIEMKTCEWPKSHTLWTDGIEESDLIIPKSLAGPLSHHNTREGYRTQM KGPWHSEELEIRFEECPGTKVHVEETCGTRGPSLRSTTASGRVIEEWCCRECTMPPL SFRAKDGCWYGMEIRPRKEPESNLVRSMVT (SEQ ID NO: 1).

[00114] In some embodiments, the amino acid sequence of the NS1 polypeptide has at least 80%, at least 81%, at least 82%, at least 83%, at least 84%,at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity with the sequence of SEQ ID NO: 1. In some embodiments, the amino acid sequence of the NS1 polypeptide may be from the amino acid sequence encoded by the sequence of GenBank Accession number KU501215.1 (SEQ ID NO: 2). In some embodiments, the amino acid sequence of the NS1 polypeptide may be amino acid positions 795 to 1145 of the amino acid sequence encoded by the sequence of GenBank Accession number KU501215.1. In some embodiments, the amino acid sequence of the NS1 polypeptide may be from Zika virus strain PRVABC59.

[00115] "Sequence Identity", "% sequence identity", "% identity", "% identical" or "sequence alignment" means a comparison of a first amino acid sequence to a second amino acid sequence, or a comparison of a first nucleic acid sequence to a second nucleic acid sequence and is calculated as a percentage based on the comparison. The result of this calculation can be described as "percent identical" or "percent ID."

[00116] Generally, a sequence alignment can be used to calculate the sequence identity by one of two different approaches. In the first approach, both mismatches at a single position and gaps at a single position are counted as non-identical positions in final sequence identity calculation. In the second approach, mismatches at a single position are counted as non-identical positions in final sequence identity calculation; however, gaps at a single position are not counted (ignored) as non-identical positions in final sequence identity calculation. In other words, in the second approach gaps are ignored in final sequence identity calculation. The difference between these two approaches, i.e. counting

gaps as non-identical positions vs ignoring gaps, at a single position can lead to variability in the sequence identity value between two sequences.

[00117] A sequence identity is determined by a program, which produces an alignment, and calculates identity counting both mismatches at a single position and gaps at a single position as non-identical positions in final sequence identity calculation. For example program Needle (EMBOS), which has implemented the algorithm of Needleman and Wunsch (Needleman and Wunsch, 1970, J. Mol. Biol. 48: 443-453), and which calculates sequence identity per default settings by first producing an alignment between a first sequence and a second sequence, then counting the number of identical positions over the length of the alignment, then dividing the number of identical residues by the length of an alignment, then multiplying this number by 100 to generate the % sequence identity [% sequence identity = (# of Identical residues / length of alignment) x 100)].

[00118] A sequence identity can be calculated from a pairwise alignment showing both sequences over the full length, so showing the first sequence and the second sequence in their full length ("Global sequence identity"). For example, program Needle (EMBOSS) produces such alignments; % sequence identity = (# of identical residues / length of alignment) x 100)].

[00119] A sequence identity can be calculated from a pairwise alignment showing only a local region of the first sequence or the second sequence ("Local Identity"). For example, program Blast (NCBI) produces such alignments; % sequence identity = (# of Identical residues / length of alignment) x 100)].

[00120] The sequence alignment is preferably generated by using the algorithm of Needleman and Wunsch (J. Mol. Biol. (1979) 48, p. 443-453). Preferably, the program "NEEDLE" (The European Molecular Biology Open Software Suite (EMBOSS)) is used with the programs default parameter (gap open=10.0, gap extend=0.5 and matrix=EBLOSUM62 for proteins and matrix=EDNAFULL for nucleotides). Then, a sequence identity can be calculated from the alignment showing both sequences over the full length, so showing the first sequence and the second sequence in their full length ("Global sequence identity"). For example: % sequence identity = (# of identical residues / length of alignment) x 100)].

[00121] In some embodiments, the at least one non-human cell adaptation mutation occurs at one or more amino acid positions within the NS1 polypeptide. In some embodiments, the mutation occurs at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1 when aligned to SEQ ID NO: 1 using a pairwise alignment algorithm. In some embodiments, the mutation at position 98 is a tryptophan to glycine substitution.

[00122] In some embodiments, the Zika virus comprises a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1. A position corresponding to position 98 of SEQ ID NO:1 can be determined by aligning the amino acid sequence of an NS-1 protein to SEQ ID NO: 1 using a pairwise alignment algorithm. Amino acid residues in viruses other than Zika virus which correspond to the tryptophan residue at position 98 of SEQ ID NO:1 are shown in Figure 7 of the present application where these residues are boxed. In some embodiments, the mutation at position 98 is a tryptophan to glycine substitution. In some embodiments, the mutation at position 98 is a tryptophan to glycine substitution at position 98 of SEQ ID NO:1.

[00123] In some embodiments, antigens of the present disclosure contain at least one non-human cell adaptation mutation within the NS1 protein, and contain at least one mutation (e.g., at least one adaptation mutation) within one or more of the C, prM, E, NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 viral proteins. In some embodiments, antigens of the present disclosure contain one or more non-human cell adaptation mutations within the NS1 protein, and do not contain at least one mutation (e.g., at least one non-human cell adaptation mutation) within one or more of the C, prM, E, NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 viral proteins. In some embodiments, antigens of the present disclosure contain at least one non-human cell adaptation mutation within the NS1 protein and do not contain at least one mutation (*e.g.,* at least one non-human cell adaptation mutation) within the envelope protein E. In some embodiments, antigens of the present disclosure include whole, inactivated virus that contains at least one non-human cell adaptation mutation in Zika virus Non-structural protein 1 (NS1), and do not include a mutation in Zika virus envelope protein E (Env). In some embodiments, antigens of the present disclosure contain a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1 and do not contain any mutation within the envelope protein E. In some embodiments, antigens of the present disclosure include whole, inactivated virus that

contains a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1 and do not include a mutation in Zika virus envelope protein E (Env). In some embodiments, whole, inactivated virus contains at least one mutation in Zika virus Non-structural protein 1 (NS1) and the sequence encoding the envelope protein is the same as the corresponding sequence in SEQ ID No. 2. In some embodiments, the Zika virus contains a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1 and the sequence encoding the envelope protein is the same as the corresponding sequence in SEQ ID No. 2. In some embodiments, whole, inactivated Zika virus contains a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1 and the sequence encoding the envelope protein is the same as the corresponding sequence in SEQ ID No. 2.

[00124] In some embodiments, antigens of the present disclosure, such as Zika virus, contain at least one non-human cell adaptation mutation that enhances genetic stability as compared to a Zika virus lacking the at least one adaptation mutation. In some embodiments, antigens of the present disclosure, such as Zika virus, contain at least one non-human cell adaptation mutation that enhances viral replication as compared to a Zika virus lacking the at least one adaptation mutation. In some embodiments, antigens of the present disclosure, such as Zika virus, contain at least one non-human cell adaptation mutation reduces or otherwise inhibits the occurrence of undesirable mutations, such as within the envelope protein E (Env) of the Zika virus.

[00125] In the above embodiments of the present disclosure, an exemplary pairwise alignment algorithm is the Needleman-Wunsch global alignment algorithm, using default parameters (e.g. with Gap opening penalty=10.0, and with Gap extension penalty=0.5, using the EBLOSUM62 scoring matrix). This algorithm is conveniently implemented in the needle tool in the EMBOSS package.

[00126] In some embodiments, antigens of the present disclosure from a Zika virus may be used in any of the vaccines and immunogenic compositions of the present disclosure. For example, the antigens of the present disclosure may be useful for treating or preventing Zika virus infection in a subject in need thereof and/or inducing an immune response, such as a protective immune response, against Zika virus in a subject in need thereof.

Production of Vaccines and Immunogenic Compositions

[00127] Other aspects of the present disclosure relate to Zika virus vaccines and immunogenic compositions containing one or more antigens of the present disclosure from at least one Zika virus. Such vaccines and immunogenic compositions may be useful, for example, for treating or preventing Zika virus infection in a subject in need thereof and/or inducing an immune response, such as a protective immune response, against Zika virus in a subject in need thereof. Vaccines and/or immunogenic compositions of the present disclosure may include, without limitation, purified viruses, inactivated viruses, attenuated viruses, recombinant viruses, purified and/or recombinant viral proteins for subunit vaccines. Vaccines and/or immunogenic compositions of the present disclosure may further include a purified antigen vaccine or immunogenic composition, a subunit vaccine or immunogenic composition, an inactivated whole virus vaccine or immunogenic composition, or a purified inactivated whole virus vaccine or immunogenic composition or an attenuated virus vaccine or immunogenic composition.

[00128] Production of vaccines and/or immunogenic compositions of the present disclosure includes growth of Zika virus, with antigens being prepared from the grown virus. Growth in cell culture is a method for preparing vaccines and/or immunogenic compositions of the present disclosure. Cells for viral growth may be cultured in suspension or in adherent conditions.

[00129] Cell lines suitable for growth of the at least one virus of the present disclosure are preferably of mammalian origin, and include, but are not limited to: insect cells (e.g., mosquito cells as described herein, VERO cells (from monkey kidneys), horse, cow (e.g. MDBK cells), sheep, dog (e.g. MDCK cells from dog kidneys, ATCC CCL34 MDCK (NBL2) or MDCK 33016, deposit number DSM ACC 2219 as described in WO97/37001), cat, and rodent (e.g. hamster cells such as BHK21-F, HKCC cells, or Chinese hamster ovary cells (CHO cells)), and may be obtained from a wide variety of developmental stages, including for example, adult, neonatal, fetal, and embryo. In certain embodiments, the cells are immortalized (e.g. PERC.6 cells, as described in WO 01/38362 and WO 02/40665, and as deposited under ECACC deposit number 96022940). In preferred embodiments, mammalian cells are utilized, and may be selected from and/or derived from one or more of the following non-limiting cell types: fibroblast cells (e.g. dermal, lung), endothelial cells (e.g. aortic, coronary, pulmonary, vascular, dermal microvascular,

umbilical), hepatocytes, keratinocytes, immune cells (e.g. T cell, B cell, macrophage, NK, dendritic), mammary cells (e.g. epithelial), smooth muscle cells (e.g. vascular, aortic, coronary, arterial, uterine, bronchial, cervical, retinal pericytes), melanocytes, neural cells (e.g. astrocytes), prostate cells (e.g. epithelial, smooth muscle), renal cells (e.g. epithelial, mesangial, proximal tubule), skeletal cells (e.g. chondrocyte, osteoclast, osteoblast), muscle cells (e.g. myoblast, skeletal, smooth, bronchial), liver cells, retinoblasts, and stromal cells. WO97/37000 and WO97/37001 describe production of animal cells and cell lines that are capable of growth in suspension and in serum free media and are useful in the production and replication of viruses.

[00130] Culture conditions for the above cell types are known and described in a variety of publications. Alternatively culture medium, supplements, and conditions may be purchased commercially, such as for example, described in the catalog and additional literature of Cambrex Bioproducts (East Rutherford, N.J.).

[00131] In certain embodiments, the cells used in the methods described herein are cultured in serum free and/or protein free media. A medium is referred to as a serum-free medium in the context of the present disclosure in which there are no additives from serum of human or animal origin. Protein-free is understood to mean cultures in which multiplication of the cells occurs with exclusion of proteins, growth factors, other protein additives and non-serum proteins, but can optionally include proteins such as trypsin or other proteases that may be necessary for viral growth. The cells growing in such cultures naturally contain proteins themselves.

[00132] Known serum-free media include Iscove's medium, Ultra-CHO medium (BioWhittaker) or EX-CELL (JRH Bioscience). Ordinary serum-containing media include Eagle's Basal Medium (BME) or Minimum Essential Medium (MEM) (Eagle, Science, 130, 432 (1959)) or Dulbecco's Modified Eagle Medium (DMEM or EDM), which are ordinarily used with up to 10% fetal calf serum or similar additives. Optionally, Minimum Essential Medium (MEM) (Eagle, Science, 130, 432 (1959)) or Dulbecco's Modified Eagle Medium (DMEM or EDM) may be used without any serum containing supplement. Protein-free media like PF-CHO (JHR Bioscience), chemically-defined media like ProCHO 4CDM (BioWhittaker) or SMIF 7 (Gibco/BRL Life Technologies) and mitogenic peptides like Primactone, Pepticase or HyPep.TM. (all from Quest International) or lactalbumin hydrolysate (Gibco and other manufacturers) are also adequately known in the prior art.

The media additives based on plant hydrolysates have the special advantage that contamination with viruses, mycoplasma or unknown infectious agents can be ruled out.

[00133] Cell culture conditions (temperature, cell density, pH value, etc.) are variable over a very wide range owing to the suitability of the cell line employed according to the present disclosure and can be adapted to the requirements of particular viral strains.

[00134] The method for propagating virus in cultured cells generally includes the steps of inoculating the cultured cells with the strain to be cultured, cultivating the infected cells for a desired time period for virus propagation, such as for example as determined by virus titer or antigen expression (e.g. between 24 and 168 hours after inoculation) and collecting the propagated virus. In some embodiments, the virus is collected via plaque purification. The cultured cells are inoculated with a virus (measured by PFU or TCID50) to cell ratio of 1:500 to 1:1, preferably 1:100 to 1:5. The virus is added to a suspension of the cells or is applied to a monolayer of the cells, and the virus is absorbed on the cells for at least 10 minutes, at least 20 minutes, at least 30 minutes, at least 40 minutes, at least 50 minutes, at least 60 minutes but usually less than 300 minutes at 25°C to 40°C, preferably 28°C to 38°C. The infected cell culture (e.g. monolayers) may be removed either by freeze-thawing or by enzymatic action to increase the viral content of the harvested culture supernatants. The harvested fluids are then either inactivated or stored frozen. Cultured cells may be infected at a multiplicity of infection ("MOI") of about 0.0001 to 10, preferably 0.002 to 5, more preferably to 0.001 to 2. Still more preferably, the cells are infected at an MOI of about 0.01. Infected cells may be harvested from 30 to 60 hours post infection, or 3 to 10 days post infection. In certain preferred embodiments, the cells are harvested 3 to 7 days post infection. More preferably, the cells are harvested 3 to 5 days post infection. In some embodiments, proteases (e.g., trypsin) may be added during cell culture to allow viral release, and the proteases may be added at any suitable stage during the culture. Alternatively, in certain embodiments, the supernatant of infected cell cultures may be harvested and the virus may be isolated or otherwise purified from the supernatant.

[00135] The viral inoculum and the viral culture are preferably free from (i.e. will have been tested for and given a negative result for contamination by) herpes simplex virus, respiratory syncytial virus, parainfluenza virus 3, SARS coronavirus, adenovirus, rhinovirus, reoviruses, polyomaviruses, birnaviruses, circoviruses, and/or parvoviruses [WO2006/027698].

[00136] Where virus has been grown on a cell line then it is standard practice to minimize the amount of residual cell line DNA in the final vaccine, in order to minimize any oncogenic activity of the host cell DNA. Contaminating DNA can be removed during vaccine preparation using standard purification procedures e.g. chromatography, etc. Removal of residual host cell DNA can be enhanced by nuclease treatment e.g. by using a DNase. A convenient method for reducing host cell DNA contamination disclosed in references (Lundblad (2001) Biotechnology and Applied Biochemistry 34:195-197, Guidance for Industry: Bioanalytical Method Validation. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Veterinary Medicine (CVM). May 2001.) involves a two-step treatment, first using a DNase (e.g. Benzonase), which may be used during viral growth, and then a cationic detergent (e.g. CTAB), which may be used during virion disruption. Removal by β-propiolactone treatment can also be used. In one embodiment, the contaminating DNA is removed by benzonase treatment of the culture supernatant.

Production of Antigens

[00137] Antigens of the present disclosure for use in vaccines and/or immunogenic compositions including, without limitation, purified viruses, inactivated viruses, inactivated whole viruses, attenuated viruses, recombinant viruses, or purified and/or recombinant viral proteins for subunit vaccines to treat and/or prevent Zika virus infection and/or induce an immune response, such as a protective immune response, against Zika virus, may be produced and/or purified or otherwise isolated by any suitable method known in the art. Antigens of the present disclosure may include, without limitation, whole virus, attenuated virus, inactivated virus, inactivated whole viruses, proteins, polypeptides (including active proteins and individual polypeptide epitopes within proteins), glycopolypeptides, lipopolypeptides, peptides, polysaccharides, polysaccharide conjugates, peptide and non-peptide mimics of polysaccharides and other molecules, small molecules, lipids, glycolipids, and carbohydrates produced, derived, purified, and/or otherwise isolated from a Zika virus. For example, suitable antigens may include, without limitation, structural polypeptides such as C, prM, and/or E, and non-structural polypeptides, such as NS1, NS2A, NS2B, NS3, NS4A, NS4B, and/or NS5 from Zika virus.

[00138] In one embodiment, the antigen of the present disclosure is a purified inactivated whole Zika virus.

[00139] Antigen of the present disclosure may be synthesized chemically or enzymatically, produced recombinantly, isolated from a natural source, or a combination of the foregoing. In certain embodiments, antigens of the present disclosure are produced, purified, isolated, and/or derived from at least one Zika virus of the present disclosure. Antigens of the present disclosure may be purified, partially purified, or a crude extract. In some embodiments, antigens of the present disclosure are viruses, such as inactivated viruses, produced as described in the above section entitled "Production of Vaccines and Immunogenic Compositions."

[00140] In certain embodiments, one or more antigens of the present disclosure may be produced by culturing a non-human cell. Cell lines suitable for production of the one or more antigens of the present disclosure may include insect cells (e.g., any of the mosquito cells described herein). Cell lines suitable for production of the one or more antigens of the present disclosure may also be cells of mammalian origin, and include, but are not limited to: VERO cells (from monkey kidneys), horse, cow (e.g. MDBK cells), sheep, dog (e.g. MDCK cells from dog kidneys, ATCC CCL34 MDCK (NBL2) or MDCK 33016, deposit number DSM ACC 2219 as described in WO97/37001), cat, and rodent (e.g. hamster cells such as BHK21-F, HKCC cells, or Chinese hamster ovary cells (CHO cells)), and may be obtained from a wide variety of developmental stages, including for example, adult, neonatal, fetal, and embryo. In certain embodiments, the cells are immortalized (e.g. PERC.6 cells, as described in WO01/38362 and WO02/40665, and as deposited under ECACC deposit number 96022940). In preferred embodiments, mammalian cells are utilized, and may be selected from and/or derived from one or more of the following non-limiting cell types: fibroblast cells (e.g. dermal, lung), endothelial cells (e.g. aortic, coronary, pulmonary, vascular, dermal microvascular, umbilical), hepatocytes, keratinocytes, immune cells (e.g. T cell, B cell, macrophage, NK, dendritic), mammary cells (e.g. epithelial), smooth muscle cells (e.g. vascular, aortic, coronary, arterial, uterine, bronchial, cervical, retinal pericytes), melanocytes, neural cells (e.g. astrocytes), prostate cells (e.g. epithelial, smooth muscle), renal cells (e.g. epithelial, mesangial, proximal tubule), skeletal cells (e.g. chondrocyte, osteoclast, osteoblast), muscle cells (e.g. myoblast, skeletal, smooth, bronchial), liver cells, retinoblasts, and stromal cells. WO97/37000 and WO97/37001 describe production of animal cells and cell lines that capable of growth in suspension and in serum free media and are useful in the production of viral antigens. In certain embodiments, the non-human cell is cultured in serum-free media.

[00141] Polypeptide antigens may be isolated from natural sources using standard methods of protein purification known in the art, including, but not limited to, liquid chromatography (e.g., high performance liquid chromatography, fast protein liquid chromatography, etc.), size exclusion chromatography, gel electrophoresis (including one-dimensional gel electrophoresis, two-dimensional gel electrophoresis), affinity chromatography, or other purification technique. In many embodiments, the antigen is a purified antigen, e.g., from about 50% to about 75% pure, from about 75% to about 85% pure, from about 85% to about 90% pure, from about 90% to about 95% pure, from about 95% to about 98% pure, from about 98% to about 99% pure, or greater than 99% pure. The purity of the purified antigen can be determined by size exclusion chromatography and the %-purity corresponds to the % of the main peak to the total area under the curve. The main peak of the purified antigen in the size exclusion chromatography may be more than 85% of the total area under the curve in the size exclusion chromatography, or more than 90% of the total area under the curve in the size exclusion chromatography, or more than 95%, or more than 98% or more than 99% of the total area under the curve in the size exclusion chromatography. Such results are considered as “purified” antigen within the meaning of this invention.

[00142] In accordance with the above disclosure regarding purity, the term "purified Zika virus" means that the main peak of the purified Zika virus in the size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography, or more than 90% of the total area under the curve in the size exclusion chromatography, or more than 95%, more than 98% or more than 99% of the total area under the curve in the size exclusion chromatography.

[00143] In accordance with the above disclosure regarding purity, the term "purified inactivated whole Zika virus" means that the main peak of the purified inactivated whole Zika virus in the size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography, or more than 90% of the total area under the curve in the size exclusion chromatography, or more than 95%, more than 98% or more than 99% of the total area under the curve in the size exclusion chromatography.

[00144] One may employ solid phase peptide synthesis techniques, where such techniques are known to those of skill in the art. See Jones, The Chemical Synthesis of Peptides (Clarendon Press, Oxford) (1994). Generally, in such methods a peptide is

produced through the sequential addition of activated monomeric units to a solid phase bound growing peptide chain.

[00145] Well-established recombinant DNA techniques can be employed for production of polypeptides, where, e.g., an expression construct comprising a nucleotide sequence encoding a polypeptide is introduced into an appropriate host cell (e.g., a eukaryotic host cell grown as a unicellular entity in in vitro cell culture, e.g., a yeast cell, an insect cell, a mammalian cell, etc.) or a prokaryotic cell (e.g., grown in in vitro cell culture), generating a genetically modified host cell; under appropriate culture conditions, the protein is produced by the genetically modified host cell.

[00146] Besides killed and attenuated virus immunogenic compositions, one can use a subunit immunogenic composition or other type of immunogenic composition which presents to the animal the antigenic components of Zika virus. The antigenic component may be a protein, glycoprotein, lipid-conjugated protein or glycoprotein, a modified lipid moiety, or other viral component which, when injected into a human, stimulates an immune response in the human such that the human develops protective immunity against Zika virus. For a subunit immunogenic composition, the virus can be cultured on mammalian cells, as described above. The cell culture can be homogenized and an immunogenic composition can be isolated by passage of the cell culture homogenate over the appropriate column or through the appropriate pore size filter or via centrifugation of the cell culture homogenate.

[00147] If the antigenic component is a protein, then one can isolate the nucleic acid which encodes that protein and generate an immunogenic composition that contains that isolated nucleic acid. The nucleic acid encoding the antigenic component can be placed on a plasmid downstream of a signal sequence of a eukaryotic promoter. That plasmid can contain one or more selectable markers and be transfected into an attenuated prokaryotic organism, such as Salmonella spp., Shigella spp., or other suitable bacteria. The bacteria can then be administered to the human so that the human can generate a protective immune response to the antigenic component. Alternatively, the nucleic acid encoding the antigenic component can be placed downstream of a prokaryotic promoter, have one or more selectable markers, and be transfected into an attenuated prokaryotic organism such as Salmonella spp., Shigella spp., or other suitable bacteria. The bacteria can then be

administered to the eukaryotic subject for which immune response to the antigen of interest is desired. See, for example, U.S. Pat. No. 6,500,419.

[00148] For a subunit immunogenic composition, the nucleic acid encoding a proteinaceous antigenic component of a Zika virus can be cloned into a plasmid such as those described in International Patent Application Publication Number WO 00/32047 (Galen) and International Patent Application Publication Number WO 02/083890 (Galen). Then the plasmid can be transfected into bacteria and the bacteria can produce the desired antigenic protein. One can isolate and purify the desired antigenic protein by a variety of methods described in both patent applications.

Virus Inactivation

[00149] Certain aspects of the present disclosure relate to Zika virus vaccines and immunogenic compositions containing one or more antigens from a Zika virus. Vaccines and/or immunogenic compositions of the present disclosure may include a purified virus, a whole virus, a recombinant virus, a live attenuated whole virus or, preferably, an inactivated whole virus, or subunits, polypeptides, and/or antigens from an inactivated virus. As such, certain embodiments of the present disclosure relate to Zika virus vaccines and/or immunogenic compositions containing one or more antigens from at least one inactivated Zika virus.

[00150] Methods of inactivating or killing viruses to destroy their ability to infect mammalian cells but do not destroy the structure of the virus are known in the art. Such methods include both chemical and physical means. Suitable means for inactivating a virus include, without limitation, treatment with an effective amount of one or more agents selected from detergents, formalin (also referred to herein as "formaldehyde"), beta-propiolactone (BPL), binary ethylamine (BEI), acetyl ethyleneimine, heat, electromagnetic radiation, x-ray radiation, gamma radiation, ultraviolet radiation (UV radiation),UV-A radiation, UV-B radiation, UV-C radiation, methylene blue, psoralen, carboxyfullerene (C60) and any combination of any thereof.

[00151] In certain embodiments of the present disclosure the at least one virus is chemically inactivated. Agents for chemical inactivation and methods of chemical inactivation are well-known in the art and described herein. In some embodiments, the at least one virus is chemically inactivated with one or more of BPL, formalin, or BEI. In

certain embodiments where the at least one virus is chemically inactivated with BPL, the virus may contain one or more modifications. In some embodiments, the one or more modifications may include a modified nucleic acid. In some embodiments, the modified nucleic acid is an alkylated nucleic acid. In other embodiments, the one or more modifications may include a modified polypeptide. In some embodiments, the modified polypeptide contains a modified amino acid residue including one or more of a modified cysteine, methionine, histidine, aspartic acid, glutamic acid, tyrosine, lysine, serine, and threonine.

[00152] In certain embodiments where the at least one virus is chemically inactivated with formalin, the inactivated virus may contain one or more modifications. In some embodiments, the one or more modifications may include a modified polypeptide. In some embodiments, the one or more modifications may include a cross-linked polypeptide. In some embodiments where the at least one virus is chemically inactivated with formalin, the vaccine or immunogenic composition further includes formalin. In certain embodiments where the at least one virus is chemically inactivated with BEI, the virus may contain one or more modifications. In some embodiments, the one or more modifications may include a modified nucleic acid. In some embodiments, the modified nucleic acid is an alkylated nucleic acid.

[00153] In some embodiments where the at least one virus is chemically inactivated with formalin, any residual unreacted formalin may be neutralized with sodium metabisulfite, may be dialyzed out, and/or may be buffer exchanged to remove the residual unreacted formalin. In some embodiments, the sodium metabisulfite is added in excess. In some embodiments, the solutions may be mixed using a mixer, such as an in-line static mixer, and subsequently filtered or further purified (e.g., using a cross flow filtrations system).

[00154] Certain embodiments of the present disclosure relate to a method for inactivating a Zika virus preparation. In some embodiments, the method involves (a) isolating, followed by purification the Zika virus preparation from one or more non-human cells that are used to produce the virus preparation and (b) treating the virus preparation with an effective amount of formalin. In certain embodiments, treating with an effective amount of formalin includes, without limitation, treating with formalin in an amount that ranges from about 0.001% v/v to about 3.0% v/v. For example, treating with an effective

amount of formalin may include treating with formalin in an amount that ranges from about 0.001% to about 3.0% v/v, about 0.005% to about 2.0% v/v, or about 0.01% to about 1.0% v/v, or in an amount of about 0.001%, about 0.0025%, about 0.005%, about 0.0075%, about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, about 0.06%, about 0.07%, about 0.08%, about 0.09%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 1.25%, about 1.5%, about 1.75%, about 2.0%, about 2.25%, about 2.5%, about 2.75%, or about 3.0% v/v.

[00155] In certain embodiments of the method, the Zika virus preparation is treated with formalin at a temperature that ranges from about 2ºC to about 42ºC. For example, the Zika virus preparation may be treated with formalin at a temperature that ranges from about 2ºC to about 42ºC, about 2ºC to about 8ºC, about 15ºC to about 37ºC. about 17ºC to about 27ºC, about 20ºC to about 25ºC, or at a temperature of about 2ºC, about 4ºC, about 8ºC, about 10ºC, about 15ºC, about 17ºC, about 18ºC, about 19ºC, about 20ºC, about 21ºC, about 22ºC, about 23ºC, about 24ºC, about 25ºC, about 26ºC, about 27ºC, about 28ºC, about 29ºC, about 30ºC, about 37ºC, or about 42ºC. In some embodiments, the Zika virus preparation is treated with formalin at room temperature.

[00156] In some embodiments, the Zika virus preparation is treated with formalin for at least about 1 day. For example, the Zika virus preparation may be treated with formalin for at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, and e.g. for no more than 15 days, e.g. from 5 to 15 days. For example, the Zika virus preparation may be treated with formalin for at least about 7 days, at least about 8 days, at least about 9 das, at least about 10 days, at least about 11 days, at least about 12 days, at least about 13 days, at least about 14 days, at least about 15 days, at least about 16 days, at least about 17 days, at least about 18 days, at least about 19 days, at least about 20 days, at least about 21 days, at least about 22 days, at least about 23 days, at least about 24 days, at least about 25 days, at least about 26 days, at least about 27 days, at least about 28 days, at least about 29 days, at least about 30 days, or more. In some embodiments, the Zika virus preparation is treated with formalin for at least about 9 days. In some embodiments, the Zika virus preparation is treated with formalin for at least about 11 days. In some embodiments, the Zika virus preparation is treated with formalin for at least about 14 days. In some embodiments, the Zika virus preparation is treated with

formalin for at least about 20 days. In some embodiments, the Zika virus preparation is treated with formalin for at least about 30 days.

[00157] In some embodiments, the method further involves neutralizing unreacted formalin with an effective amount of sodium metabisulfite. In some embodiments, the effective amount of sodium metabisulfite ranges from about 0.01 mM to about 100 mM. For example, the sodium metabisulfite may be added at an effective concentration of from about 0.01 mM to about 100 mM, from about 0.1 mM to about 50 mM, from about 0.5 mM to about 20mM, or from about 1 mM to about 10 mM, or at a concentration of about 0.01mM, about 0.05mM, about 0.1mM, about 0.25mM, about 0.5mM, about 0.75mM, about 1mM, about 2mM, about 3mM, about 4mM, about 5mM, about 6mM, about 7mM, about 8mM, about 9mM, about 10mM, about 20mM, about 30mM about 40mM, about 50mM, about 75mM or about 100mM. In some embodiments, the formalin is neutralized with about 2mM sodium metabisulfite.

[00158] In some embodiments, the method involves (a) isolating followed by purification the Zika virus preparation from one or more non-human cells that are used to produce the virus preparation; (b) treating the virus preparation with an effective amount of formalin; (c) neutralizing the virus preparation with an effective amount of sodium metabisulfite; and (d) purifying the neutralized virus preparation. Any method of purifying a virus preparation known in the art may be employed, including, without limitation, using cross flow filtration (CFF), multimodal chromatography, size exclusion chromatography, cation exchange chromatography, and/or anion exchange chromatography. In some embodiments, the neutralized virus preparation is purified by cross flow filtration (CFF). In some embodiments, the virus preparation is purified to a high degree in an amount that is about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95% about 96%, about 97%, about 98%, about 99%, or more.

[00159] Certain embodiments of the present disclosure relate thus to Zika virus vaccines and/or immunogenic compositions containing a purified inactivated whole Zika virus. The term "inactivated whole Zika virus" as used herein is intended to comprise a Zika virus which has been treated with an inactivating method such as treatment with an effective amount of formalin. Such a treatment is considered not to destroy the structure of the virus, i.e. do not destroy the secondary, tertiary or quaternary structure and immunogenic epitopes of the virus, but the inactivated Zika virus is no longer able to infect

host cells which can be infected with a Zika virus which has not been inactivated. In one embodiment, the inactivated Zika virus is no longer able to infect VERO cells and exert a cytopathic effect on the VERO cells.

[00160] The method for determining the completeness of inactivation of an arbovirus preparation comprises the steps of:

(i) inoculating insect cells with an arbovirus preparation which was subjected to an inactivation step and incubating the insect cells for a first period of time, thereby producing an insect cell supernatant;

(ii) inoculating mammalian cells with the insect cell supernatant produced in (i) and incubating the mammalian cells for a second period of time; and

(iii)determining whether the virus preparation contains a residual replicating virus that produces a cytopathic effect on the mammalian cells.

Inactivation is considered complete in case no residual replication virus can be detected such a by plaques.

[00161] For the present disclosure the term "inactivated whole Zika virus" thus refers to a Zika virus obtainable from a method wherein the Zika virus is treated with formalin in an amount that ranges from about 0.001% v/v to about 3.0% v/v from 5 to 15 days at a temperature that ranges from about 15ºC to about 37ºC, in particular 0.02 % v/v formaldehyde for 10 days at 22 °C or in particular 0.01 % v/v formaldehyde for 10 days at 22 °C. The definition is meant to encompass Zika virus obtained from a method wherein the Zika virus is treated with formalin in an amount that ranges from about 0.001% v/v to about 3.0% v/v from 5 to 15 days at a temperature that ranges from about 15ºC to about 37ºC , in particular 0.02 % v/v formaldehyde for 10 days at 22 °C or in particular 0.01 % v/v formaldehyde for 10 days at 22 °C, but is not to be understood to be limited to those, since other methods may lead to the same inactivated whole Zika virus. In certain such embodiments, however, the Zika virus is obtained from a method wherein the Zika virus is treated with formalin in an amount that ranges from about 0.001% v/v to about 3.0% v/v from 5 to 15 days at a temperature that ranges from about 15ºC to about 37ºC, in particular 0.02 % v/v formaldehyde for 10 days at 22 °C or in particular 0.01 % v/v formaldehyde for 10 days at 22 °C.

[00162] Alternatively, within the present disclosure "inactivated whole Zika virus" thus refers to a Zika virus that has been tested by the method comprising the steps (i) to (iii) and does not show any plaque formation in step (iii):

(i) inoculating insect cells with an arbovirus preparation which was subjected to an inactivation step and incubating the insect cells for a first period of time, thereby producing an insect cell supernatant;

(ii) inoculating mammalian cells with the insect cell supernatant produced in (i) and incubating the mammalian cells for a second period of time; and

(iii)determining whether the virus preparation contains a residual replicating virus that produces a cytopathic effect on the mammalian cells.

[00163] The term "purified inactivated whole Zika virus" thus refers to a Zika virus obtainable or obtained from a method wherein the Zika virus is treated with formalin in an amount that ranges from about 0.001% v/v to about 3.0% v/v from 5 to 15 days at a temperature that ranges from about 15ºC to about 37ºC , in particular 0.02 % v/v formaldehyde for 10 days at 22 °C or in particular 0.01 % v/v formaldehyde for 10 days at 22 °C, or alternatively by the above mentioned method for determining the completeness of inactivation and, if required, has been subjected to a purification process. The purified Zika virus has therefore a lower content of host cell proteins such as Vero cell proteins and host cell DNA such as Vero cell DNA than a non-purified Zika virus. The term "purified inactivated whole Zika virus" thus refers to a Zika virus obtainable or obtained from a method wherein the Zika virus is treated with formalin in an amount that ranges from about 0.001% v/v to about 3.0% v/v from 5 to 15 days at a temperature that ranges from about 15ºC to about 37ºC, in particular 0.02 % v/v formaldehyde for 10 days at 22 °C or in particular 0.01 % v/v formaldehyde for 10 days at 22 °C, or alternatively by the above mentioned method for determining the completeness of inactivation and, provides a main peak of at least 85% of the total area under the curve in the size exclusion chromatography.

[00164] In certain such embodiments the purified inactivated whole Zika virus is furthermore a clonal isolate obtained or obtainable by plaque purification.

[00165] In certain such embodiments the purified inactivated whole Zika virus, which is optionally furthermore a clonal isolate obtained or obtainable by plaque

purification, contains a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1 and does not contain any mutation within the envelope protein E. In certain such embodiments the mutation is a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1. In certain such embodiments the Zika virus is derived from strain PRVABC59. In certain such embodiments the Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2.

[00166] The vaccines and/or immunogenic compositions of the present disclosure containing one or more antigens from at least one inactivated Zika virus may be useful for treating or preventing Zika virus infection in a subject in need thereof and/or inducing an immune response, such as a protective immune response, against Zika virus in a subject in need thereof.

Adjuvants

[00167] Other aspects of the present disclosure relate to Zika virus vaccines and/or immunogenic compositions containing one or more antigens from at least one Zika virus described herein in combination with one or more adjuvants. Such adjuvanted vaccines and/or immunogenic compositions of the present disclosure may be useful for treating or preventing Zika virus infection in a subject in need thereof and/or inducing an immune response, such as a protective immune response, against Zika virus in a subject in need thereof.

[00168] Various methods of achieving an adjuvant effect for vaccines are known and may be used in conjunction with the Zika virus vaccines and/or immunogenic compositions disclosed herein. General principles and methods are detailed in "The Theory and Practical Application of Adjuvants", 1995, Duncan E. S. Stewart-Tull (ed.), John Wiley & Sons Ltd, ISBN 0-471-95170-6, and also in "Vaccines: New Generation Immunological Adjuvants", 1995, Gregoriadis G et al. (eds.), Plenum Press, New York, ISBN 0-306-45283-9.

[00169] In some embodiments, a Zika virus vaccine or immunogenic composition includes the antigens and an adjuvant. Antigens may be in a mixture with at least one adjuvant, at a weight-based ratio of from about 10:1 to about 10^{10}:1 antigen:adjuvant, e.g., from about 10:1 to about 100:1, from about 100:1 to about 10^3:1, from about 10^3:1 to about 10^4:1, from about 10^4:1 to about 10^5:1, from about 10^5:1 to about 10^6:1, from about 10^6:1 to

about 10^7:1, from about 10^7:1 to about 10^8:1, from about 10^8:1 to about 10^9:1, or from about 10^9:1 to about 10^{10}:1 antigen:adjuvant. One of skill in the art can readily determine the appropriate ratio through information regarding the adjuvant and routine experimentation to determine optimal ratios.

[00170] Exemplary adjuvants may include, but are not limited to, aluminum salts, calcium phosphate, toll-like receptor (TLR) agonists, monophosphoryl lipid A (MLA), MLA derivatives, synthetic lipid A, lipid A mimetics or analogs, cytokines, saponins, muramyl dipeptide (MDP) derivatives, CpG oligos, lipopolysaccharide (LPS) of gram-negative bacteria, polyphosphazenes, emulsions (oil emulsions), chitosan, vitamin D, stearyl or octadecyl tyrosine, virosomes, cochleates, poly(lactide-co-glycolides) (PLG) microparticles, poloxamer particles, microparticles, liposomes, Complete Freund's Adjuvant (CFA), and Incomplete Freund's Adjuvant (IFA). In some embodiments, the adjuvant is an aluminum salt.

[00171] In some embodiments, the adjuvant includes at least one of alum, aluminum phosphate, aluminum hydroxide, potassium aluminum sulfate, and Alhydrogel 85. In some embodiments, aluminum salt adjuvants of the present disclosure have been found to increase adsorption of the antigens of the Zika virus vaccines and/or immunogenic compositions of the present disclosure. Accordingly, in some embodiments, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% of the antigen is adsorbed to the aluminum salt adjuvant.

[00172] In some embodiments, the vaccine or immunogenic composition includes an aluminum salt adjuvant (e.g., alum) from about 100 µg to about 600 µg, from about 100 µg to about 500 µg, from about 125 µg to about 500 µg, from about 150 µg to about 500 µg, from about 175 µg to about 500 µg, from about 100 µg to about 450 µg, from about 125 µg to about 450 µg, from about 150 µg to about 450 µg, from about 175 µg to about 450 µg, from about 100 µg to about 400 µg, from about 125 µg to about 400 µg, from about 150 µg to about 400 µg, from about 175 µg to about 400 µg, from about 100 µg to about 350µg, from about 125 µg to about 350µg, from about 150 µg to about 350µg, from about 175 µg to about 350µg, from about 100 µg to about 300 µg, from about 125 µg to about 300 µg, from about 150 µg to about 300 µg, from about 175 µg to about 300 µg, from about 100 µg

to about 250 µg, from about 125 µg to about 250 µg, from about 150 µg to about 250 µg, from about 175 µg to about 250 µg, from about 100 µg to about 225 µg, from about 125 µg to about 225 µg, from about 150 µg to about 225 µg, from about 175 µg to about 225 µg, or about 200 µg. In some embodiments the vaccine or immunogenic composition includes an aluminum salt adjuvant (e.g., alum such as aluminum hydroxide) at about 100 µg to about 600µg at about 100 µg to about 300µg or about 150µg to about 250µg or about 200 µg.

[00173] In some embodiments, the vaccines and/or immunogenic compositions contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of a purified inactivated whole Zika virus such as a Zika virus with a mutation which is a tryptophan to glycine substitution at position 98 of SEQ ID NO:1 or at a position corresponding to position 98 of SEQ ID NO:1 as described herein in combination with one or more adjuvants, such as 100 µg to about 600µg or about 150µg to about 250µg or about 200 µg alum, such as aluminum hydroxide.

[00174] In some embodiments, the vaccine or immunogenic composition contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 in combination with one or more adjuvants, such as 100 µg to about 600µg or about 150µg to about 250µg or about 200 µg alum, such as aluminum hydroxide.

[00175] In some embodiments, the vaccine or immunogenic composition contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2 in combination with one or more adjuvants, such as 100 µg to about 600µg or about 150µg to about 250µg or about 200 µg alum, such as aluminum hydroxide.

[00176] In some embodiments, the vaccine or immunogenic composition contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of a purified inactivated whole plaque purified Zika virus isolate comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2 in

combination with one or more adjuvants, such as 100 µg to about 600µg or about 150µg to about 250µg or about 200 µg alum, such as aluminum hydroxide.

[00177] Certain embodiments of the present disclosure include a method for preparing an adjuvanted Zika virus vaccine or immunogenic composition, which involves (a) mixing the vaccine or immunogenic composition with an aluminum salt adjuvant, with the vaccine or immunogenic composition including one or more antigens from at least one Zika virus described herein and (b) incubating the mixture under suitable conditions for a period of time that ranges from about 1 hour to about 24 hours (e.g., about 16 hours to about 24 hours), with at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% of the antigen adsorbed to the aluminum salt adjuvant. In certain embodiments of the method, the at least one Zika virus is a Zika virus comprising a non-human cell adaptation mutation (e.g., a non-human cell adaptation mutation in protein NS1 such as a Trp98Gly mutation.

[00178] In some embodiments of the method, the mixture is incubated at a temperature that ranges from about 2°C to about 8°C. In some embodiments of the method, the mixture is incubated under constant mixing using any suitable mixer known in the art. In some embodiments of the method, the mixture is incubated at pH that ranges in value from about 6.5 to about 8.5, from about 6.5 to about 8, from about 6.8 to about 7.8, from about 6.9 to about 7.6, from about 7 to about 7.5, from about 6.8 to about 8.5, from about 6.9 to about 8.5, or from about 7 to about 8.5. In certain preferred embodiments, the mixture is incubated at a neutral pH. In some embodiments of the method, the aluminum salt adjuvant is selected from alum, aluminum phosphate, aluminum hydroxide, potassium aluminum sulfate, and Alhydrogel 85.

[00179] Monophosphoryl Lipid A (MLA), a non-toxic derivative of lipid A from Salmonella, is a potent TLR-4 agonist that has been developed as a vaccine adjuvant (Evans et al. (2003) Expert Rev. Vaccines 2(2): 219-229). In pre-clinical murine studies intranasal MLA has been shown to enhance secretory, as well as systemic, humoral responses (Baldridge et al. (2000) Vaccine 18(22): 2416-2425; Yang et al. (2002) Infect. Immun. 70(7): 3557-3565). It has also been proven to be safe and effective as a vaccine adjuvant in clinical studies of greater than 120,000 patients (Baldrick et al. (2002) Regul. Toxicol.

Pharmacol. 35(3): 398-413; Baldrick et al. (2004) J. Appl. Toxicol. 24(4): 261-268). MLA stimulates the induction of innate immunity through the TLR-4 receptor and is thus capable of eliciting nonspecific immune responses against a wide range of infectious pathogens, including both gram negative and gram positive bacteria, viruses, and parasites (Baldrick et al. (2004) J. Appl. Toxicol. 24(4): 261-268; Persing et al. (2002) Trends Microbiol. 10(10 Suppl): S32-37). Inclusion of MLA in intranasal formulations should provide rapid induction of innate responses, eliciting nonspecific immune responses from viral challenge while enhancing the specific responses generated by the antigenic components of the vaccine.

[00180] Accordingly, in one embodiment, the present disclosure provides a composition comprising monophosphoryl lipid A (MLA), 3 De-O-acylated monophosphoryl lipid A (3D-MLA), or a derivative thereof as an enhancer of adaptive and innate immunity. Chemically 3D-MLA is a mixture of 3 De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains. A preferred form of 3 De-O-acylated monophosphoryl lipid A is disclosed in European Patent 0 689 454 B1 (SmithKline Beecham Biologicals SA). In another embodiment, the present disclosure provides a composition comprising synthetic lipid A, lipid A mimetics or analogs, such as BioMira's PET Lipid A, or synthetic derivatives designed to function like TLR-4 agonists.

[00181] Additional exemplary adjuvants include, without limitation, polypeptide adjuvants that may be readily added to the antigens described herein by co-expression with the polypeptide components or fusion with the polypeptide components to produce chimeric polypeptides. Bacterial flagellin, the major protein constituent of flagella, is an adjuvant which has received increasing attention as an adjuvant protein because of its recognition by the innate immune system by the toll-like receptor TLR5. Flagellin signaling through TLR5 has effects on both innate and adaptive immune functions by inducing DC maturation and migration as well as activation of macrophages, neutrophils, and intestinal epithelial cells resulting in production of pro-inflammatory mediators.

[00182] TLR5 recognizes a conserved structure within flagellin monomers that is unique to this protein and is required for flagellar function, precluding its mutation in response to immunological pressure. The receptor is sensitive to a 100 fM concentration but does not recognize intact filaments. Flagellar disassembly into monomers is required for binding and stimulation.

[00183] As an adjuvant, flagellin has potent activity for induction of protective responses for heterologous antigens administered either parenterally or intranasally and adjuvant effects for DNA vaccines have also been reported. A Th2 bias is observed when flagellin is employed which would be appropriate for a respiratory virus such as influenza but no evidence for IgE induction in mice or monkeys has been observed. In addition, no local or systemic inflammatory responses have been reported following intranasal or systemic administration in monkeys. The Th2 character of responses elicited following use of flagellin is somewhat surprising since flagellin signals through TLR5 in a MyD88-dependent manner and all other MyD88-dependent signals through TLRs have been shown to result in a Th1 bias. Importantly, pre-existing antibodies to flagellin have no appreciable effect on adjuvant efficacy making it attractive as a multi-use adjuvant.

[00184] A common theme in many recent intranasal vaccine trials is the use of adjuvants and/or delivery systems to improve vaccine efficacy. In one such study an influenza H3 vaccine containing a genetically detoxified E. coli heat-labile enterotoxin adjuvant (LT R192G) resulted in heterosubtypic protection against H5 challenge but only following intranasal delivery. Protection was based on the induction of cross neutralizing antibodies and demonstrated important implications for the intranasal route in development of new vaccines.

[00185] Cytokines, colony-stimulating factors (e.g., GM-CSF, CSF, and the like); tumor necrosis factor; interleukin-2, -7, -12, interferons and other like growth factors, may also be used as adjuvants as they may be readily included in the Zika virus vaccines or immunogenic compositions by admixing or fusion with the polypeptide component.

[00186] In some embodiments, the Zika virus vaccine and/or immunogenic compositions disclosed herein may include other adjuvants that act through a Toll-like receptor such as a nucleic acid TLR9 ligand comprising a 5'-TCG-3' sequence; an imidazoquinoline TLR7 ligand; a substituted guanine TLR7/8 ligand; other TLR7 ligands such as Loxoribine, 7-deazadeoxyguanosine, 7-thia-8-oxodeoxyguanosine, Imiquimod (R-837), and Resiquimod (R-848).

[00187] Certain adjuvants facilitate uptake of the vaccine molecules by APCs, such as dendritic cells, and activate these. Non-limiting examples are selected from the group consisting of an immune targeting adjuvant; an immune modulating adjuvant such as a

toxin, a cytokine, and a mycobacterial derivative; an oil formulation; a polymer; a micelle forming adjuvant; a saponin; an immunostimulating complex matrix (ISCOM matrix); a particle; DDA; aluminum adjuvants; DNA adjuvants; MLA; and an encapsulating adjuvant.

[00188] Additional examples of adjuvants include agents such as aluminum salts such as hydroxide or phosphate (alum), commonly used as 0.05 to 0.1 percent solution in buffered saline (see, e.g., Nicklas (1992) Res. Immunol. 143:489-493), admixture with synthetic polymers of sugars (e.g. Carbopol®) used as 0.25 percent solution, aggregation of the protein in the vaccine by heat treatment with temperatures ranging between 70° to 101°C for 30 second to 2 minute periods respectively and also aggregation by means of cross-linking agents are possible. Aggregation by reactivation with pepsin treated antibodies (Fab fragments) to albumin, mixture with bacterial cells such as C. parvum or endotoxins or lipopolysaccharide components of gram-negative bacteria, emulsion in physiologically acceptable oil vehicles such as mannide mono-oleate (Aracel A) or emulsion with 20 percent solution of a perfluorocarbon (Fluosol-DA) used as a block substitute may also be employed. Admixture with oils such as squalene and IFA may also be used.

[00189] DDA (dimethyldioctadecylammonium bromide) is an interesting candidate for an adjuvant, but also Freund's complete and incomplete adjuvants as well as quillaja saponins such as QuilA and QS21 are interesting. Further possibilities include poly[di(earboxylatophenoxy)phosphazene (PCPP) derivatives of lipopolysaccharides such as monophosphoryl lipid A (MLA), muramyl dipeptide (MDP) and threonyl muramyl dipeptide (tMDP). The lipopolysaccharide based adjuvants may also be used for producing a predominantly Th1-type response including, for example, a combination of monophosphoryl lipid A, such as 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt.

[00190] Liposome formulations are also known to confer adjuvant effects, and therefore liposome adjuvants may be used in conjunction with the Zika virus vaccines and/or immunogenic compositions.

[00191] Immunostimulating complex matrix type (ISCOM® matrix) adjuvants may also be used with the Zika virus vaccine antigens and immunogenic compositions, especially since it has been shown that this type of adjuvants are capable of up-regulating

MHC Class II expression by APCs. An ISCOM matrix consists of (optionally fractionated) saponins (triterpenoids) from Quillaja saponaria, cholesterol, and phospholipid. When admixed with the immunogenic protein such as the Zika virus vaccine or immunogenic composition antigens, the resulting particulate formulation is what is known as an ISCOM particle where the saponin may constitute 60-70% w/w, the cholesterol and phospholipid 10-15% w/w, and the protein 10-15% w/w. Details relating to composition and use of immunostimulating complexes can for example be found in the above-mentioned text-books dealing with adjuvants, but also Morein B et al. (1995) Clin. Immunother. 3: 461-475 as well as Barr I G and Mitchell G F (1996) Immunol. and Cell Biol. 74: 8-25 provide useful instructions for the preparation of complete immunostimulating complexes.

[00192] The saponins, whether or not in the form of iscoms, that may be used in the adjuvant combinations with the Zika virus vaccines and immunogenic compositions disclosed herein include those derived from the bark of Quillaja Saponaria Molina, termed Quil A, and fractions thereof, described in U.S. Pat. No. 5,057,540 and "Saponins as vaccine adjuvants", Kensil, C. R. (1996)Crit Rev Ther Drug Carrier Syst 12 (1-2):1-55; and EP 0 362 279 B1. Exemplary fractions of Quil A are QS21, QS7, and QS17.

[00193] β-Escin is another hemolytic saponins for use in the adjuvant compositions of the Zika virus vaccines and/or immunogenic compositions. Escin is described in the Merck index (12th ed: entry 3737) as a mixture of saponins occurring in the seed of the horse chestnut tree, Lat: Aesculus hippocastanum. Its isolation is described by chromatography and purification (Fiedler, Arzneimittel-Forsch. 4, 213 (1953)), and by ion-exchange resins (Erbring et al., U.S. Pat. No. 3,238,190). Fractions of escin have been purified and shown to be biologically active (Yoshikawa M, et al. (Chem Pharm Bull (Tokyo) 1996 August; 44(8):1454-1464)). β-escin is also known as aescin.

[00194] Another hemolytic saponin for use in the Zika virus vaccines and/or immunogenic compositions is Digitonin. Digitonin is described in the Merck index (12th Edition, entry 3204) as a saponin, being derived from the seeds of Digitalis purpurea and purified according to the procedure described Gisvold et al. (1934) J.Am.Pharm.Assoc. 23: 664; and Ruhenstroth-Bauer (1955)Physiol.Chem., 301, 621. Its use is described as being a clinical reagent for cholesterol determination.

[00195] Another interesting possibility of achieving adjuvant effect is to employ the technique described in Gosselin et al., 1992. In brief, the presentation of a relevant antigen such as an antigen in a Zika virus vaccine and/or immunogenic composition of the present disclosure can be enhanced by conjugating the antigen to antibodies (or antigen binding antibody fragments) against the FC receptors on monocytes/macrophages. Especially conjugates between antigen and anti-FCRI have been demonstrated to enhance immunogenicity for the purposes of vaccination. The antibody may be conjugated to the Zika virus vaccine or immunogenic composition antigens after generation or as a part of the generation including by expressing as a fusion to any one of the polypeptide components of the Zika virus vaccine and/or immunogenic composition antigens. Other possibilities involve the use of the targeting and immune modulating substances (e.g., cytokines). In addition, synthetic inducers of cytokines such as poly I:C may also be used.

[00196] Suitable mycobacterial derivatives may be selected from the group consisting of muramyl dipeptide, complete Freund's adjuvant, RIBI, (Ribi ImmunoChem Research Inc., Hamilton, Mont.) and a diester of trehalose such as TDM and TDE.

[00197] Examples of suitable immune targeting adjuvants include CD40 ligand and CD40 antibodies or specifically binding fragments thereof (cf. the discussion above), mannose, a Fab fragment, and CTLA-4.

[00198] Examples of suitable polymer adjuvants include a carbohydrate such as dextran, PEG, starch, mannan, and mannose; a plastic polymer; and latex such as latex beads.

[00199] Yet another interesting way of modulating an immune response is to include the immunogen (optionally together with adjuvants and pharmaceutically acceptable carriers and vehicles) in a “virtual lymph node” (VLN) (a proprietary medical device developed by ImmunoTherapy, Inc., 360 Lexington Avenue, New York, N.Y. 10017-6501). The VLN (a thin tubular device) mimics the structure and function of a lymph node. Insertion of a VLN under the skin creates a site of sterile inflammation with an upsurge of cytokines and chemokines. T- and B-cells as well as APCs rapidly respond to the danger signals, home to the inflamed site and accumulate inside the porous matrix of the VLN. It has been shown that the necessary antigen dose required to mount an immune response to an antigen is reduced when using the VLN, and that immune protection conferred by

vaccination using a VLN surpassed conventional immunization using Ribi as an adjuvant. The technology is described briefly in Gelber C et al., 1998, "Elicitation of Robust Cellular and Humoral Immune Responses to Small Amounts of Immunogens Using a Novel Medical Device Designated the Virtual Lymph Node", in: "From the Laboratory to the Clinic, Book of Abstracts, Oct. 12-15, 1998, Seascape Resort, Aptos, Calif."

[00200] Oligonucleotides may be used as adjuvants in conjunction with the Zika virus vaccine and/or immunogenic composition antigens and may contain two or more dinucleotide CpG motifs separated by at least three or more or even at least six or more nucleotides. CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Pat. Nos. 6,008,200 and 5,856,462.

[00201] Such oligonucleotide adjuvants may be deoxynucleotides. In certain embodiments, the nucleotide backbone in the oligonucleotide is phosphorodithioate, or a phosphorothioate bond, although phosphodiester and other nucleotide backbones such as PNA including oligonucleotides with mixed backbone linkages may also be used. Methods for producing phosphorothioate oligonucleotides or phosphorodithioate are described in U.S. Pat. No. 5,666,153, U.S. Pat. No. 5,278,302 and WO 95/26204.

[00202] Exemplary oligonucleotides have the following sequences. The sequences may contain phosphorothioate modified nucleotide backbones:

[00203] (SEQ ID NO: 3) OLIGO 1: TCC ATG ACG TTC CTG ACG TT (CpG 1826);

[00204] (SEQ ID NO: 4) OLIGO 2: TCT CCC AGC GTG CGC CAT (CpG 1758);

[00205] (SEQ ID NO: 5) OLIGO 3: ACC GAT GAC GTC GCC GGT GAC GGC ACC ACG;

[00206] (SEQ ID NO: 6) OLIGO 4: TCG TCG TTT TGT CGT TTT GTC GTT (CpG 2006); and

[00207] (SEQ ID NO: 7) OLIGO 5: TCC ATG ACG TTC CTG ATG CT (CpG 1668)

[00208] Alternative CpG oligonucleotides include the above sequences with inconsequential deletions or additions thereto. The CpG oligonucleotides as adjuvants may be synthesized by any method known in the art (e.g., EP 468520). For example, such oligonucleotides may be synthesized utilizing an automated synthesizer. Such oligonucleotide adjuvants may be between 10-50 bases in length. Another adjuvant system involves the combination of a CpG-containing oligonucleotide and a saponin derivative particularly the combination of CpG and QS21 is disclosed in WO 00/09159.

[00209] Many single or multiphase emulsion systems have been described. One of skill in the art may readily adapt such emulsion systems for use with a Zika virus vaccine and/or immunogenic composition antigens so that the emulsion does not disrupt the antigen's structure. Oil in water emulsion adjuvants per se have been suggested to be useful as adjuvant compositions (EP 399 843B), also combinations of oil in water emulsions and other active agents have been described as adjuvants for vaccines (WO 95/17210; WO 98/56414; WO 99/12565; WO 99/11241). Other oil emulsion adjuvants have been described, such as water in oil emulsions (U.S. Pat. No. 5,422,109; EP 0 480 982 B2) and water in oil in water emulsions (U.S. Pat. No. 5,424,067; EP 0 480 981 B).

[00210] The oil emulsion adjuvants for use with the Zika virus vaccines and/or immunogenic compositions described herein may be natural or synthetic, and may be mineral or organic. Examples of mineral and organic oils will be readily apparent to one skilled in the art.

[00211] In order for any oil in water composition to be suitable for human administration, the oil phase of the emulsion system may include a metabolizable oil. The meaning of the term metabolizable oil is well known in the art. Metabolizable can be defined as "being capable of being transformed by metabolism" (Dorland's Illustrated Medical Dictionary, W.B. Sanders Company, 25th edition (1974)). The oil may be any vegetable oil, fish oil, animal oil or synthetic oil, which is not toxic to the recipient and is capable of being transformed by metabolism. Nuts (such as peanut oil), seeds, and grains are common sources of vegetable oils. Synthetic oils may also be used and can include commercially available oils such as NEOBEE® and others. Squalene (2,6,10,15,19,23-Hexamethyl-2,6,10,14,18,22-tetracosahexaene) is an unsaturated oil which is found in large quantities in shark-liver oil, and in lower quantities in olive oil, wheat germ oil, rice bran oil, and yeast, and may be used with the Zika virus vaccine and/or immunogenic

compositions. Squalene is a metabolizable oil virtue of the fact that it is an intermediate in the biosynthesis of cholesterol (Merck index, 10th Edition, entry no.8619).

[00212] Exemplary oil emulsions are oil in water emulsions, and in particular squalene in water emulsions.

[00213] In addition, the oil emulsion adjuvants for use with the Zika virus vaccine and/or immunogenic compositions may include an antioxidant, such as the oil α-tocopherol (vitamin E, EP 0 382 271 B1).

[00214] WO 95/17210 and WO 99/11241 disclose emulsion adjuvants based on squalene, α-tocopherol, and TWEEN 80 (TM), optionally formulated with the immunostimulants QS21 and/or 3D-MLA. WO 99/12565 discloses an improvement to these squalene emulsions with the addition of a sterol into the oil phase. Additionally, a triglyceride, such as tricaprylin (C27H50O6), may be added to the oil phase in order to stabilize the emulsion (WO 98/56414).

[00215] The size of the oil droplets found within the stable oil in water emulsion may be less than 1 micron, may be in the range of substantially 30-600 nm, substantially around 30-500 nm in diameter, or substantially 150-500 nm in diameter, and in particular about 150 nm in diameter as measured by photon correlation spectroscopy. In this regard, 80% of the oil droplets by number may be within these ranges, more than 90% or more than 95% of the oil droplets by number are within the defined size ranges. The amounts of the components present in oil emulsions are conventionally in the range of from 2 to 10% oil, such as squalene; and when present, from 2 to 10% alpha tocopherol; and from 0.3 to 3% surfactant, such as polyoxyethylene sorbitan monooleate. The ratio of oil: alpha tocopherol may be equal or less than 1 as this provides a more stable emulsion. SPAN 85 (TM) may also be present at a level of about 1%. In some cases it may be advantageous that the Zika virus vaccines and/or immunogenic compositions disclosed herein will further contain a stabilizer.

[00216] The method of producing oil in water emulsions is well known to one skilled in the art. Commonly, the method includes the step of mixing the oil phase with a surfactant such as a PBS/TWEEN80® solution, followed by homogenization using a homogenizer, it would be clear to one skilled in the art that a method comprising passing the mixture twice through a syringe needle would be suitable for homogenizing small volumes of liquid.

Equally, the emulsification process in microfluidizer (M110S microfluidics machine, maximum of 50 passes, for a period of 2 minutes at maximum pressure input of 6 bar (output pressure of about 850 bar)) could be adapted by one skilled in the art to produce smaller or larger volumes of emulsion. This adaptation could be achieved by routine experimentation comprising the measurement of the resultant emulsion until a preparation was achieved with oil droplets of the required diameter.

[00217] Alternatively the Zika virus vaccines and/or immunogenic compositions may be combined with vaccine vehicles composed of chitosan (as described above) or other polycationic polymers, polylactide and polylactide-coglycolide particles, poly-N-acetyl glucosamine-based polymer matrix, particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene ether or ester, in either a non-particulate solution or suspension, or in a particulate structure such as a paucilamelar liposome or ISCOM.

[00218] Additional illustrative adjuvants for use in the Zika virus vaccines and/or immunogenic compositions as described herein include SAF (Chiron, Calif., United States), MF-59 (Chiron, see, e.g., Granoff et al. (1997) Infect Immun. 65 (5):1710-1715), the SBAS series of adjuvants (e.g., SB-AS2 (an oil-in-water emulsion containing MLA and QS21); SBAS-4 (adjuvant system containing alum and MLA), available from SmithKline Beecham, Rixensart, Belgium), Detox (Enhanzyn®) (GlaxoSmithKline), RC-512, RC-522, RC-527, RC-529, RC-544, and RC-560 (GlaxoSmithKline) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. patent application Ser. Nos. 08/853,826 and 09/074,720.

[00219] Other examples of adjuvants include, but are not limited to, Hunter's TiterMax® adjuvants (CytRx Corp., Norcross, Ga.); Gerbu adjuvants (Gerbu Biotechnik GmbH, Gaiberg, Germany); nitrocellulose (Nilsson and Larsson (1992) Res. Immunol. 143:553-557); alum (e.g., aluminum hydroxide, aluminum phosphate) emulsion based formulations including mineral oil, non-mineral oil, water-in-oil or oil-in-water emulsions, such as the Seppic ISA series of Montamide adjuvants (e.g., ISA-51, ISA-57, ISA-720, ISA-151, etc.; Seppic, Paris, France); and PROVAX® (IDEC Pharmaceuticals); OM-174 (a

glucosamine disaccharide related to lipid A); Leishmania elongation factor; non-ionic block copolymers that form micelles such as CRL 1005; and Syntex Adjuvant Formulation. See, e.g., O'Hagan et al. (2001) Biomol Eng. 18(3):69-85; and "Vaccine Adjuvants: Preparation Methods and Research Protocols" D. O'Hagan, ed. (2000) Humana Press.

[00220] Other exemplary adjuvants include adjuvant molecules of the general formula: $HO(CH_2CH_2O)n\text{-}A\text{-}R$, (I) where, n is 1-50, A is a bond or --C(O)--, R is C1-50 alkyl or Phenyl C1-50 alkyl.

[00221] One embodiment consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), where n is between 1 and 50, 4-24, or 9; the R component is C1-50, C4-C20 alkyl, or C12 alkyl, and A is a bond. The concentration of the polyoxyethylene ethers should be in the range 0.1-20%, from 0.1-10%, or in the range 0.1-1%. Exemplary polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-steoryl ether, polyoxyethylene-8-steoryl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Polyoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck index (12th edition: entry 7717). These adjuvant molecules are described in WO 99/52549.

[00222] The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, an adjuvant combination may include the CpG as described above.

[00223] Further examples of suitable pharmaceutically acceptable excipients for use with the Zika virus vaccines and/or immunogenic compositions disclosed herein include water, phosphate buffered saline, isotonic buffer solutions.

Virus purification

[00224] Further aspects of the present disclosure relate to methods of purifying Zika virus. In some embodiments, the method includes inoculating a plurality of cells with an inoculum containing a population of Zika viruses, and obtaining from one or more of the inoculated cells a Zika virus clonal isolate by plaque purification. In some embodiments, the cells are non-human cells (e.g., insect cells, mammalian cells, etc.). In some embodiments, the cells are insect cells (such as any of the mosquito cells/cell lines

described herein). In some embodiments, the cells are mammalian cells (such as any of the mammalian cells/cell lines described herein). In some embodiments, the mammalian cells are monkey cells.

[00225] In some embodiments, the population of Zika virus is heterogeneous (e.g., comprising two or more genotypes). In some embodiments, the population of Zika viruses comprises a Zika virus clonal isolate (e.g., from strain PRVABC59) and/or one or more Zika viruses that have been previously passaged in cell culture. In some embodiments, plaque purification (e.g., as described herein) allows for the substantial and/or complete separation of a (genetically homogenous) clonal isolate from a heterogeneous viral population. In some embodiments, the monkey cells are from a VERO cell line (e.g., VERO 10-87 cells). In some embodiments, the inoculum comprises human serum. In some embodiments, the inoculum comprises one or more adventitious agents (e.g., one or more contamination viruses). In some embodiments, plaque purification (e.g., as described herein) allows for the substantial and/or complete purification of a (genetically homogenous) clonal isolate away from one or more adventitious agents.

[00226] In some embodiments, the methods described for isolating and/or purifying a Zika virus clonal includes one or more (e.g., one or more, two or more, three or more, four or more, five or more, etc.) additional plaque purifications of the Zika virus clonal isolate. In some embodiments, the methods described for isolating and/or purifying a Zika virus clonal isolate includes passaging the Zika virus clonal isolate one or more (e.g., one or more, two or more, three or more, four or more, five or more, etc.) times in cell culture (e.g., in insect cells such as a mosquito cell line and/or in mammalian cells such as a VERO cell line).

[00227] Further aspects of the present disclosure relate to methods of purifying Zika virus for the preparation of a vaccine or immunogenic composition. In some embodiments, the methods include one or more (e.g., one or more, two or more, three or more, four or more, five or more, or six) steps of (in any order, including the following order): performing depth filtration of a sample or preparation containing a Zika virus; buffer exchanging and/or diluting a sample containing a Zika virus (e.g., by cross flow filtration (CFF)) to produce a retentate; binding a sample comprising a Zika virus to an ion exchange membrane (e.g., an anion exchange membrane, a cation exchange membrane) to produce a bound fraction, where the bound fraction comprises the Zika virus, and eluting the bound

fraction from the ion exchange membrane; treating a sample containing a Zika virus with an effective amount of any of the chemical inactivators described herein; neutralizing a sample containing a chemically inactivated Zika virus with sodium metabisulfite; and/or purifying a neutralized sample comprising a chemically inactivated Zika virus (e.g., by cross flow filtration (CFF)). In some embodiments, the method includes the steps of (a) passing a sample containing a Zika virus through a first depth filter to produce a first eluate, where the first eluate contains the Zika virus; (b) buffer exchanging and/or diluting the first eluate by cross flow filtration (CFF) to produce a first retentate, where the first retentate contains the Zika virus; (c) binding the first retentate to an ion exchange membrane to produce a first bound fraction, where the first bound fraction contains the Zika virus, and eluting the first bound fraction from the ion exchange membrane to produce a second eluate, where the second eluate contains the Zika virus; (d) passing the second eluate through a second depth filter to produce a second retentate, wherein the second retentate contains the Zika virus; (e) treating the second retentate with an effective amount of a chemical inactivator; (f) neutralizing the treated second retentate with sodium metabisulfite; and (g) purifying the neutralized second retentate by cross flow filtration (CFF).

[00228] Depth filters may be applied in a cartridge or capsule format, such as with the SUPRACAP™ series of depth filter capsules (Pall Corporation) using a Bio 20 SEITZ® depth filter sheet. Other suitable depth filtration techniques and apparatuses are known in the art and include Sartorius PP3 filters. In some embodiments, the depth filter has a pore size of between about 0.2µm and about 3µm. In some embodiments, the pore size of the depth filter is less than about any of the following pore sizes (in µm): 3, 2.8, 2.6, 2.4, 2.2, 2.0, 1.8, 1.6, 1.4, 1.2, 1.0, 0.8, 0.6, and 0.4. In some embodiments, the pore size of the depth filter is greater than about any of the following pore sizes (in µm): 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, or 2.8. That is, the pore size of the depth filter can be any of a range of pore sizes (in µm) having an upper limit of 3, 2.8, 2.6, 2.4, 2.2, 2.0, 1.8, 1.6, 1.4, 1.2, 1.0, 0.8, 0.6, and 0.4 and an independently selected lower limit of 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, or 2.8; wherein the lower limit is less than the upper limit.

[00229] As described herein, cation exchange and anion exchange chromatography may be used in the methods of the present disclosure to purify a Zika virus harvested from a cell of the present disclosure. For example, clarified viral harvest may be basified, loaded

onto an anion exchange membrane, eluted by salt or pH, filtered, and inactivated. This is only an exemplary scheme, and one of skill in the art may readily contemplate variants thereof with substituted, deleted, inserted, or reordered steps.

[00230] Anion and cation exchange chromatography both rely on the attraction of charged macromolecules of interest (e.g., a virus) in a mobile phase to a substrate having an opposite charge. In cation exchange chromatography, the negatively charged substrate or membrane attracts positively charged macromolecules. In anion exchange chromatography, the positively charged substrate or membrane attracts negatively charged macromolecules. Once macromolecules are bound or loaded onto the substrate, they may be eluted in linear or step-wise fashion from the substrate in a manner dependent on their characteristics, thereby enacting a separation of differently charged molecules. This principle may be used to purify viruses from other macromolecules. Elution may be effected by varying pH or salt content of the mobile phase buffer. Elution may be gradient or step-wise. As described herein, elution may be effected using a change in pH of the mobile phase or by using a change in ionic strength of the mobile phase (e.g., through addition of a salt). A variety of salts are used for elution, including without limitation sodium chloride, potassium chloride, sodium sulphate, potassium sulphate, ammonium sulphate, sodium acetate, potassium phosphate, calcium chloride, and magnesium chloride. In certain embodiments, the salt is NaCl. A variety of suitable buffers are known in the art and described herein. Viral purification methods using ion exchange chromatography are also generally known; see, e.g., purification of influenza virus available online at www.pall.com/pdfs/Biopharmaceuticals/MustangQXT_AcroPrep_USD2916.pdf.

[00231] A variety of devices known in the art are suitable for cation exchange chromatography (optionally including filtration), such as the Mustang® S system (Pall Corporation), which uses a cation exchange membrane with a 0.65µm pore size. A variety of functional groups are used for cation exchange membranes, including without limitation pendant sulfonic functional groups in a cross-linked, polymeric coating. A variety of buffers may be used to bind an eluate containing a Zika virus of the present disclosure to a cation exchange membrane. Exemplary buffers include, without limitation, citrate and phosphate buffers (additional buffers are described infra). In some embodiments, a buffer used in cation exchange chromatography (e.g., in loading and/or elution) contains polysorbate (e.g., TWEEN®-80 at 0.05%, 0.1%, 0.25%, or 0.5%).

[00232] A variety of devices known in the art are suitable for anion exchange chromatography (optionally including filtration), such as the Mustang® Q system (Pall Corporation), which uses an anion exchange membrane with a 0.8μm pore size. Another suitable anion exchange membrane is SartobindQ IEXNano. A variety of functional groups are used for anion exchange membranes, including without limitation pendant quaternary amine functional groups in a cross-linked, polymeric coating. A variety of buffers may be used to bind an eluate containing a Zika virus of the present disclosure to an anion exchange membrane. Exemplary buffers include, without limitation, phosphate buffer (additional buffers are described infra). In some embodiments, a buffer used in anion exchange chromatography (e.g., in loading and/or elution) contains polysorbate (e.g., TWEEN®-80 at 0.05%, 0.1%, 0.25%, or 0.5%). In some embodiments, the virus is eluted by step elution, e.g. using 250 mM NaCl, 500 mM NaCl and 750 mM NaCl.

Formulations and dose of Vaccines and/or immunogenic compositions

[00233] Further aspects of the present disclosure relate to formulations of vaccines and/or immunogenic compositions of the present disclosure containing one or more antigens from a Zika virus described herein.

[00234] Such vaccines and/or immunogenic compositions of the present disclosure containing one or more antigens from a Zika virus described herein may be useful for treating or preventing Zika virus infection in a subject in need thereof and/or inducing an immune response, such as a protective immune response, against Zika virus in a subject in need thereof.

[00235] Typically, vaccines and/or immunogenic compositions of the present disclosure are prepared as injectables either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection may also be prepared. Such preparations may also be emulsified or produced as a dry powder. The active immunogenic ingredient is often mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, sucrose, glycerol, ethanol, or the like, and combinations thereof. In addition, if desired, the vaccine or immunogenic composition may contain auxiliary substances such as wetting or emulsifying agents, pH buffering agents, or adjuvants which enhance the effectiveness of the vaccine or immunogenic composition.

[00236] Vaccines or immunogenic compositions may be conventionally administered parenterally, by injection, for example, either subcutaneously, transcutaneously, intradermally, subdermally or intramuscularly. In certain embodiments the composition is administered intramuscular or subcutaneously. Additional formulations which are suitable for other modes of administration include suppositories and, in some cases, oral, peroral, intranasal, buccal, sublingual, intraperitoneal, intravaginal, anal and intracranial formulations. For suppositories, traditional binders and carriers may include, for example, polyalkalene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, or even 1-2%.In certain embodiments, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the Zika virus vaccine and/or immunogenic composition described herein is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into conveniently sized molds and allowed to cool and to solidify.

[00237] Formulations suitable for intranasal delivery include liquids (e.g., aqueous solution for administration as an aerosol or nasal drops) and dry powders (e.g. for rapid deposition within the nasal passage). Formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, sucrose, trehalose, xylitol, and chitosan. Mucosadhesive agents such as chitosan can be used in either liquid or powder formulations to delay mucociliary clearance of intranasally-administered formulations. Sugars such as mannitol, sorbitol, trehalose, and/or sucrose can be used as stability agents in liquid formulations and as stability, bulking, or powder flow and size agents in dry powder formulations. In addition, adjuvants such as monophosphoryl lipid A (MLA), or derivatives thereof, or CpG oligonucleotides can be used in both liquid and dry powder formulations as an immunostimulatory adjuvant.

[00238] Formulations suitable for oral delivery include liquids, solids, semi-solids, gels, tablets, capsules, lozenges, and the like. Formulations suitable for oral delivery include tablets, lozenges, capsules, gels, liquids, food products, beverages, nutraceuticals, and the like. Formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, sorbitol, trehalose, polyols such as sugars such as sucrose, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. Other Zika virus vaccines and immunogenic compositions may take the form of solutions, suspensions, pills, sustained release formulations or powders and

contain 10-95% of active ingredient, or 25-70%.For oral formulations, cholera toxin is an interesting formulation partner (and also a possible conjugation partner).

[00239] The Zika virus vaccines and/or immunogenic compositions when formulated for vaginal administration may be in the form of pessaries, tampons, creams, gels, pastes, foams or sprays. Any of the foregoing formulations may contain agents in addition to Zika virus vaccine and/or immunogenic compositions, such as carriers, known in the art to be appropriate.

[00240] In some embodiments, the Zika virus vaccines and/or immunogenic compositions of the present disclosure may be formulated for systemic or localized delivery. Such formulations are well known in the art. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Systemic and localized routes of administration include, e.g., intradermal, topical application, intravenous, intramuscular, etc.

[00241] The vaccines and/or immunogenic compositions of the present disclosure may be administered in a manner compatible with the dosage formulation, and in such amount as will be therapeutically effective and immunogenic. The dosage of the antigen may range in particular from , about 1 µg to about 100 µg, about 1 µg to about 40 µg, about 1 µg to about 30 µg, about 1 µg to about 20 µg , about 1 µg to about 15 µg, or from about 2 µg to about 15 µg, or from about 5 µg to about 15 µg, or from about 10 µg to about 15 µg, The dosage may in particular be about 2µg, about 5µg, about 10µg, about 15 µg or about 20 µg, in particular about 10µg .The amount of the antigen, i.e. the purified inactivated Zika virus, can be determined by a Bradford assay (Bradford et al. (1976) Anal. Biochem. 72: 248-254) using defined amounts of recombinant Zika envelope protein to establish the standard curve. Thus the dosage of the antigen may thus also be referred to as micrograms (µg) of Zika Envelope protein E (µg Env). µg Antigen and µg Env thus mean the same within the meaning of this disclosure. In some embodiments, the vaccines and/or immunogenic compositions contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of antigen in the form of a purified inactivated whole Zika virus such as a Zika virus with a mutation which is a tryptophan to glycine substitution at position 98 of SEQ ID NO:1 or at a position corresponding to position 98 of SEQ ID NO:1 as described herein.

[00242] In some embodiments, the vaccine or immunogenic composition contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of antigen in the form of a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59.

[00243] In some embodiments, the vaccine or immunogenic composition contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of antigen in the form of a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2.

[00244] In some embodiments, the vaccine or immunogenic composition contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of antigen in the form of a purified inactivated whole plaque purified Zika virus isolate comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2.

[00245] In certain such embodiments the vaccine or immunogenic composition comprises

a dose of about 10µg of purified inactivated whole virus

about 200 µg aluminum hydroxide,

a buffer; and optionally

a sugar such as sucrose.

[00246] Suitable regimens for initial administration and booster shots are also variable but are typified by an initial administration followed by subsequent inoculations or other administrations.

[00247] The manner of application may be varied widely. Any of the conventional methods for administration of a vaccine or immunogenic composition are applicable. These include oral application on a solid physiologically acceptable base or in a physiologically acceptable dispersion, parenterally, by injection or the like for e.g. intramuscular or subcutaneous administration. The dosage of the vaccine or immunogenic composition will depend on the route of administration and may vary according to the age of the person to be

vaccinated and the formulation of the antigen. The vaccine or immunogenic composition can have a unit dosage volume of more than 0.5mL, of 0.5mL or of less than 0.5mL, as described herein. For instance, it can be administered at a volume of 0.25mL. A volume of 0.5mL are suitable for intramuscular or subcutaneous administration.

[00248] Delivery agents that improve mucoadhesion can also be used to improve delivery and immunogenicity especially for intranasal, oral or lung based delivery formulations. One such compound, chitosan, the N-deacetylated form of chitin, is used in many pharmaceutical formulations. It is an attractive mucoadhesive agent for intranasal vaccine delivery due to its ability to delay mucociliary clearance and allow more time for mucosal antigen uptake and processing. In addition, it can transiently open tight junctions which may enhance transepithelial transport of antigen to the NALT. In a recent human trial, a trivalent inactivated influenza vaccine administered intranasally with chitosan but without any additional adjuvant yielded seroconversion and HI titers that were only marginally lower than those obtained following intramuscular inoculation.

[00249] Chitosan can also be formulated with adjuvants that function well intranasally such as the genetically detoxified E. coli heat-labile enterotoxin mutant LTK63. This adds an immunostimulatory effect on top of the delivery and adhesion benefits imparted by chitosan resulting in enhanced mucosal and systemic responses.

[00250] Finally, it should be noted that chitosan formulations can also be prepared in a dry powder format that has been shown to improve vaccine stability and result in a further delay in mucociliary clearance over liquid formulations. This was seen in a recent human clinical trial involving an intranasal dry powder diphtheria toxoid vaccine formulated with chitosan in which the intranasal route was as effective as the traditional intramuscular route with the added benefit of secretory IgA responses. The vaccine was also very well tolerated. Intranasal dry powdered vaccines for anthrax containing chitosan and MLA, or derivatives thereof, induce stronger responses in rabbits than intramuscular inoculation and are also protective against aerosol spore challenge.

[00251] Intranasal vaccines represent an exemplary formulation as they can affect the upper and lower respiratory tracts in contrast to parenterally administered vaccines which are better at affecting the lower respiratory tract. This can be beneficial for inducing tolerance to allergen-based vaccines and inducing immunity for pathogen-based vaccines.

[00252] In addition to providing protection in both the upper and lower respiratory tracts, intranasal vaccines avoid the complications of needle inoculations and provide a means of inducing both mucosal and systemic humoral and cellular responses via interaction of particulate and/or soluble antigens with nasopharyngeal-associated lymphoid tissues (NALT).

[00253] Vaccines and/or immunogenic compositions of the present disclosure are pharmaceutically acceptable. They may include components in addition to the antigen and adjuvant, e.g. they will typically include one or more pharmaceutical carrier(s) and/or excipient(s). A thorough discussion of such components is available in Gennaro (2000) Remington: The Science and Practice of Pharmacy. 20th edition, ISBN: 0683306472.

[00254] To control tonicity, it is preferred to include a physiological salt, such as a sodium salt. Sodium chloride (NaCl) is preferred, which may be present at between 1 and 20 mg/ml. Other salts that may be present include potassium chloride, potassium dihydrogen phosphate, disodium phosphate dehydrate, magnesium chloride, calcium chloride, etc.

[00255] Vaccines and/or immunogenic compositions of the present disclosure may include one or more buffers. Typical buffers include: a phosphate buffer; a Tris buffer; a borate buffer; a succinate buffer; a histidine buffer (particularly with an aluminum hydroxide adjuvant); or a citrate buffer. Buffers will typically be included in the 5-20mM range.

[00256] The pH of a vaccine or immunogenic composition will generally be between 5.0 and 8.5 or 5.0 and 8.1, and more typically between 6.0 and 8.5 e.g. between 6.0 and 8.0, between 6.5 and 8.0, between 6.5 and 7.5, between 7.0 and 8.5, between 7.0 and 8.0, or between 7.0 and 7.8. A manufacturing process of the present disclosure may therefore include a step of adjusting the pH of the bulk vaccine prior to packaging.

[00257] The vaccine or immunogenic composition is preferably sterile. It is preferably non pyrogenic, e.g. containing <1 EU (endotoxin unit, a standard measure) per dose, and preferably <0.1 EU per dose. It is preferably gluten free.

[00258] In certain embodiments, the vaccines and/or immunogenic compositions of the present disclosure may include a detergent in an effective concentration. In some

embodiments, an effective amount of detergent may include without limitation, about 0.00005% v/v to about 5% v/v or about 0.0001% v/v to about 1% v/v. In certain embodiments, an effective amount of detergent is about 0.001% v/v, about 0.002% v/v, about 0.003% v/v, about 0.004% v/v, about 0.005% v/v, about 0.006% v/v, about 0.007% v/v, about 0.008% v/v, about 0.009% v/v, or about 0.01% v/v. Without wishing to be bound by theory, detergents help maintain the vaccines and/or immunogenic compositions of the present disclosure in solution and help to prevent the vaccines and/or immunogenic compositions from aggregating.

[00259] Suitable detergents include, for example, polyoxyethylene sorbitan ester surfactant (known as 'Tweens'), octoxynol (such as octoxynol-9 (Triton X 100) or t-octylphenoxypolyethoxyethanol), cetyl trimethyl ammonium bromide ('CTAB'), and sodium deoxycholate, particularly for a split or surface antigen vaccine. The detergent may be present only at trace amounts. Other residual components in trace amounts could be antibiotics (e.g. neomycin, kanamycin, polymyxin B). In some embodiments, the detergent contains polysorbate. In some embodiments, the effective concentration of detergent includes ranges from about 0.00005% v/v to about 5% v/v.

[00260] The vaccines and/or immunogenic compositions are preferably stored at between 2°C and 8°C. They should ideally be kept out of direct light. The antigen and emulsion will typically be in admixture, although they may initially be presented in the form of a kit of separate components for extemporaneous admixing. Vaccines and/or immunogenic compositions will generally be in aqueous form when administered to a subject.

Methods of the Present Disclosure

[00261] The present invention is in particular also directed to a method of treating or preventing, in particular preventing Zika virus infection and/or preventing Zika virus disease in a subject in need thereof comprising administering to a subject or a subject population a therapeutically effective amount of a vaccine or immunogenic composition as described herein.

[00262] The disease is in general mild and of short duration. Some clinical manifestations include, but are not limited to, mild fever, maculopapular rash, conjunctivitis and arthralgia. Despite mild clinical symptoms in the pregnant woman, Zika virus infection

during pregnancy has been associated with serious outcomes for the fetus and newborn. The severity of the disease is related to the consequences in the fetus and newborn child from women with Zika virus infection during pregnancy. The spectrum of congenital anomalies associated with Zika virus infection, known as Congenital Zika Syndrome (CZS), consists of severe microcephaly with partially collapsed skull, cerebral cortices with subcortical calcifications, macular scarring and focal pigmentary retinal mottling, congenital contractures, and marked early hypertonia with symptoms of extrapyramidal involvement . Furthermore the Zika virus is a neurotropic flavivirus that can potentially cause disease within the central nervous system. There is additionally a Worldwide concern over Zika virus causing Guillain-Barré Syndrome (GBS).

[00263] The prevention of the Zika virus disease thus does not only concern the subject being treated but extends to the fetus and newborn in case the subject being treated is or will be pregnant. The method according to the invention thus comprises treating the subject by administering to the subject the vaccine or immunogenic composition and the treating of the fetus and newborn by administering to a pregnant subject or a subject that intends to become pregnant or woman of childbearing potential the vaccine or immunogenic composition. In particular the subject is human.

[00264] Further aspects of the present disclosure relate to methods for using vaccines and/or or immunogenic compositions described herein containing one or more antigens from at least one Zika virus (e.g., a clonal Zika virus isolate, a Zika virus comprising a non-human cell adaptation mutation such as a non-human cell adaptation mutation in protein NS1) to treat or prevent Zika virus in a subject in need thereof and/or to induce an immune response to Zika virus in a subject in need thereof.

[00265] In certain such methods, the vaccines and/or immunogenic compositions contains a dose of 1µg to 15µg, or 2µg, or 5µg, or 10µg of a purified inactivated whole Zika virus such as a Zika virus with a mutation which is a tryptophan to glycine substitution at position 98 of SEQ ID NO:1 or at a position corresponding to position 98 of SEQ ID NO:1 as described herein optionally in combination with one or more adjuvants, such as 100 µg to about 300µg or about 150µg to about 250µg or about 200 µg alum, such as aluminum hydroxide.

[00266] In certain such methods, the vaccine or immunogenic composition contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 optionally in combination with one or more adjuvants, such as 100 µg to about 600µg or about 150µg to about 250µg or about 200 µg alum, such as aluminum hydroxide.

[00267] In certain such methods, the vaccine or immunogenic composition contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2 optionally in combination with one or more adjuvants, such as 100 µg to about 600µg or about 150µg to about 250µg or about 200 µg alum, such as aluminum hydroxide.

[00268] In certain such methods, the vaccine or immunogenic composition contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of a purified inactivated whole plaque purified Zika virus isolate comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2 optionally in combination with one or more adjuvants, such as 100 µg to about 600µg or about 150µg to about 250µg or about 200 µg alum, such as aluminum hydroxide.

[00269] In some embodiments, the present disclosure relates to methods for treating or preventing Zika virus infection in a subject in need thereof by administering to the subject a therapeutically effective amount of a vaccine and/or immunogenic composition of the present disclosure containing one or more antigens from at least one Zika virus (e.g., a clonal Zika virus isolate, a Zika virus comprising a non-human cell adaptation mutation such as a non-human cell adaptation mutation in protein NS1). In some embodiments, the present disclosure relates to methods for inducing an immune response to Zika virus in a subject in need thereof by administering to the subject a therapeutically effective amount of a vaccine and/or or immunogenic composition of the present disclosure containing one or more antigens from at least one Zika (e.g., a clonal Zika virus isolate, a Zika virus comprising a non-human cell adaptation mutation such as a non-human cell adaptation

mutation in protein NS1). In some embodiments, the administering step induces a protective immune response against Zika virus in the subject. In some embodiments, the subject is a human. In some embodiments, the subject is pregnant or intends to become pregnant or woman of childbearing potential.

[00270] The Zika virus vaccines and/or immunogenic compositions disclosed herein may be used to protect or treat a subject (e.g., a mammal such as a human) susceptible to, or suffering from a viral infection, by means of administering the vaccine by intranasal, peroral, oral, buccal, sublingual, intramuscular, intraperitoneal, intradermal, transdermal, subdermal, intravaginal, anal, intracranial, intravenous, transcutaneous, or subcutaneous administration, in particular intramuscular administration. Methods of systemic administration of the vaccines and/or immunogenic compositions of the present disclosure may include conventional syringes and needles, or devices designed for ballistic delivery of solid vaccines (WO 99/27961), or needleless pressure liquid jet device (U.S. Pat. No. 4,596,556; U.S. Pat. No. 5,993,412), or transdermal patches (WO 97/48440; WO 98/28037). The Zika virus vaccines and/or immunogenic compositions of the present disclosure may also be applied to the skin (transdermal or transcutaneous delivery WO 98/20734; WO 98/28037). The Zika virus vaccines and/or immunogenic compositions of the present disclosure therefore may include a delivery device for systemic administration, pre-filled with the Zika virus vaccine or immunogenic compositions. Accordingly there is provided methods for treating or preventing Zika virus infection and/or for inducing an immune response in a subject (e.g., a mammal such as a human), including the step of administering a vaccine or immunogenic composition of the present disclosure and optionally including an adjuvant and/or a carrier, to the subject, where the vaccine or immunogenic composition is administered via the parenteral or systemic route.

[00271] The vaccines and/or immunogenic compositions of the present disclosure may be used to protect or treat a subject (e.g., a mammal such as a human) susceptible to, or suffering from a viral infection, by means of administering the vaccine or immunogenic composition via a mucosal route, such as the oral/alimentary or nasal route. Alternative mucosal routes are intravaginal and intra-rectal. The mucosal route of administration may be via the nasal route, termed intranasal vaccination. Methods of intranasal vaccination are well known in the art, including the administration of a droplet, spray, or dry powdered form of the vaccine into the nasopharynx of the individual to be immunized. Nebulized or

aerosolized vaccine formulations are potential forms of the Zika virus vaccines and/or immunogenic compositions disclosed herein. Enteric formulations such as gastro resistant capsules and granules for oral administration, suppositories for rectal or vaginal administration are also formulations of the vaccines and/or immunogenic compositions of the present disclosure.

[00272] The Zika virus vaccines and/or immunogenic compositions of the present disclosure may also be administered via the oral route. In such cases the pharmaceutically acceptable excipient may also include alkaline buffers, or enteric capsules or microgranules. The Zika virus vaccines and/or immunogenic compositions of the present disclosure may also be administered by the vaginal route. In such cases, the pharmaceutically acceptable excipients may also include emulsifiers, polymers such as CARBOPOL®, and other known stabilizers of vaginal creams and suppositories. The Zika virus vaccines and/or immunogenic compositions may also be administered by the rectal route. In such cases the excipients may also include waxes and polymers known in the art for forming rectal suppositories.

[00273] In some embodiments, the administering step includes one or more administrations. Administration can be by a single dose schedule or a multiple dose (prime-boost) schedule. In a multiple dose schedule the various doses may be given by the same or different routes e.g. a parenteral prime and mucosal boost, a mucosal prime and parenteral boost, etc. Typically they will be given by the same route, such as by intramuscular or subcutaneous administration. Multiple doses will typically be administered at least 1 week apart (e.g. about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 16 weeks, etc., such as 1 to 16 weeks apart). Giving two doses separated by from 25-30 days (e.g. 28 days, 4 weeks) is particularly useful. In certain such embodiments the mode of administration is intramuscular or subcutaneous administration.

[00274] The methods of the present disclosure include administration of a therapeutically effective amount or an immunogenic amount of the Zika virus vaccines and/or immunogenic compositions of the present disclosure. A therapeutically effective amount or an immunogenic amount may be an amount of the vaccines and/or immunogenic compositions of the present disclosure that will induce a protective immunological response

in the uninfected, infected or unexposed subject to which it is administered. Such a response will generally result in the development in the subject of a secretory, cellular and/or antibody-mediated immune response to the vaccine. Usually, such a response includes, but is not limited to one or more of the following effects; the production of antibodies from any of the immunological classes, such as immunoglobulins A, D, E, G or M; the proliferation of B and T lymphocytes; the provision of activation, growth and differentiation signals to immunological cells; expansion of helper T cell, suppressor T cell, and/or cytotoxic T cell.

[00275] In certain such methods, the vaccines and/or immunogenic compositions contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of a purified inactivated whole Zika virus such as a Zika virus with a mutation which is a tryptophan to glycine substitution at position 98 of SEQ ID NO:1 or at a position corresponding to position 98 of SEQ ID NO:1 as described herein optionally in combination with one or more adjuvants, such as 100 µg to about 600µg or about 150µg to about 250µg or about 200 µg alum, such as aluminum hydroxide.

[00276] In certain such methods, the vaccine or immunogenic composition contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 optionally in combination with one or more adjuvants, such as 100 µg to about 600µg or about 150µg to about 250µg or about 200 µg alum, such as aluminum hydroxide.

[00277] In certain such methods, the vaccine or immunogenic composition contains a dose of 1µg to 15µg, or 2µg, 5µg or 10µg of a purified inactivated whole Zika virus comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2 optionally in combination with one or more adjuvants, such as 100 µg to about 600µg or about 150µg to about 250µg or about 200 µg alum, such as aluminum hydroxide.

[00278] In certain such methods, the vaccine or immunogenic composition contains a dose of 1µg to 15µg, or 2µg, or 5µg or 10µg of a purified inactivated whole plaque purified

Zika virus isolate comprising a Trp98Gly mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO:1, wherein the Zika virus is derived from strain PRVABC59 comprising the genomic sequence according to SEQ ID NO:2 optionally in combination with one or more adjuvants, such as 100 µg to about 600µg or about 150µg to about 250µg or about 200 µg alum, such as aluminum hydroxide.

[00279] In certain such methods the administration of the vaccine or immunogenic composition induces the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 10, or greater than 50, or greater than 100, or greater than 200 or greater than 1000, or greater than 1500, or greater than 2000, or greater than 2000, or greater than 3000, as determined by the plaque reduction neutralization test (PRNT)

[00280] In certain such methods the administration of the vaccine or immunogenic composition induces the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 300 or greater than 500, or greater than 1000, or greater than 1500, or greater than 2000, or greater than 2000, or greater than 3000, or greater than 5000, or greater than 10,000, as determined by the reporter virus particle neturalization assay (RVP).

[00281] In certain such methods the above neutralizing antibodies titers are achieved 14 and/or 28 days after the administration.

[00282] In certain such methods 14 and/or 28 days after the administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in a subject is greater than 250, as determined by the plaque reduction neutralization test (PRNT)

[00283] In certain such methods 14 and/or 28 days after the administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in a subject is greater than 1000, as determined by the reporter virus particle neturalization assay (RVP).

[00284] In certain such methods such titers are achieved 14 and/or 28 days after the administration. Such generation of neutralizing antibodies provides for a high seroconversion rates in a Zika virus seronegative population of at least 20 subjects. In

certain such embodiments the seroconversion rate is at least 60%, at least 70%, at least 80%, at least 90% at least 95% or 100%.

[00285] In certain such methods such titers are achieved 14 and/or 28 days after the administration. Such generation of naturalizing antibodies provides for high seropositvity rates in a population, in particular in a Zika virus seronegative population, of at least 20 subjects. In certain such embodiments the seropositvity rate is at least 60%, at least 70%, at least 80%, at least 90% at least 95% or 100%.

[00286] In certain such methods the seroconversion rates and/or seropositivity rates are achieved 14 and/or 28 days after the administration.

[00287] In certain such methods severe adverse events are at the same time minimized or avoided. In certain such methods fever of 39°C and higher is avoided.

[00288] According to the inventive method the vaccine or immunogenic composition is administered as a single dose or as multiple doses as e.g. in a first (prime) and a second (boost) administration.

[00289] In certain such methods 14 and/or 28 days after the single dose or prime administration of the vaccine or immunogenic composition the neutralizing antibodies titers to Zika virus in a subject, in particular a flavivirus naive subject, are greater than 200, as determined by the plaque reduction neutralization test (PRNT).

[00290] In certain such methods 14 and/or 28 days after the single dose or prime administration of the vaccine or immunogenic composition the geometric mean neutralizing antibodies titers to Zika virus in particular in a flavivirus naive population of at least 20 subjects are greater than 200, as determined by the plaque reduction neutralization test (PRNT).

[00291] In certain such methods 14 and/or 28 days after the single dose or prime administration of the vaccine or immunogenic composition the neutralizing antibodies titers to Zika virus in a subject, in particular a flavivirus naive subject, are greater than 1000, as determined by the reporter virus particle neutralization assay (RVP).

[00292] In certain such methods 14 and/or 28 days after the single dose or prime administration of the vaccine or immunogenic composition the geometric mean neutralizing

antibodies titers to Zika virus in particular in a flavivirus naive population of at least 20 subjects are greater than 1000, as determined by the reporter virus particle neutralization assay (RVP).

[00293] Such generation of neutralizing antibodies provides for a high seroconversion rates in a flavivirus naive population of at least 20 subjects after the single dose or prime administration. In certain such embodiments the seroconversion rate is at least 60%, at least 70%, at least 80%, at least 90% at least 95% or 100%.

[00294] Such generation of neutralizing antibodies provides for high seropositvity rates in a population, in particular in a flavivirus naive population, of at least 20 subjects after the single dose or prime administration. In certain such embodiments the seropositvity rate is at least 60%, at least 70%, at least 80%, at least 90% at least 95% or 100%.

[00295] In certain methods the administration comprises prime and boost administration wherein the prime and boost administration takes place from about 1 to about 16 weeks apart. In certain such methods the second (boost) administration is administered at least 28 days after the first (prime) administration.

[00296] In certain such methods 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the neutralizing antibodies titers to Zika virus in a subject, in particular a flavivirus naive subject, are greater than 1000, or greater than 1500, or greater than 3000, as determined by the plaque reduction neutralization test (PRNT)

[00297] In certain such methods 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the geometric mean neutralizing antibodies titers to Zika virus in particular in a flavivirus naive population of at least 20 subjects are greater than 1000, or greater than 1500, or greater than 3000, as determined by the plaque reduction neutralization test (PRNT)

[00298] In certain such methods 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the neutralizing antibodies titers to Zika virus in a subject, in particular a flavivirus naive subject, are greater than 3000, or greater than 5000, or greater than 10000, as determined by the reporter virus particle neutralization assay (RVP).

[00299] In certain such methods 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the geometric mean neutralizing antibodies titers to Zika virus in particular in a flavivirus naive population of at least 20 subjects are greater than 3000, or greater than 5000, or greater than 10000, as determined by the reporter virus particle neutralization assay (RVP).

[00300] Such generation of neutralizing antibodies provides for a high seroconversion rates in a flavivirus naive population of at least 20 subjects after the boost administration. In certain such embodiments the seroconversion rate is at least 60%, at least 70%, at least 80%, at least 90% at least 95% or 100%.

[00301] Such generation of neutralizing antibodies provides for high seropositvity rates in a population, in particular in a flavivirus naive population, of at least 20 subjects after the boost administration. In certain such embodiments the seropositvity rate is at least 60%, at least 70%, at least 80%, at least 90% at least 95% or

[00302] According to a certain method the subject or subject population is from a Zika endemic region. According to a certain such method the subject or subject population is from a Zika endemic region subject to an outbreak. According to a certain such method the subject or subject population is flavivirus naïve.

[00303] According to a certain method the subject or subject population is from a Zika non-endemic region. According to a certain such method the subject or subject population is from a Zika non-endemic region travelling to an endemic region. According to a certain such method the subject or subject population is flavivirus naïve.

[00304] According to a certain method the subject or subject population is Hispanic, Latino, American Indian, Alaska native, Asian, Black or African American, Native Hawaiian or White or a mixture thereof.

[00305] According to a certain method the subject or subject population is 18 to 29 years of age.

[00306] According to a certain method the subject or subject population is 30 to 49 years of age.

[00307] The vaccine or immunogenic composition as disclosed herein is also disclosed for use in a method as disclosed herein.

[00308] Also disclosed herein is the use of the vaccine or immunogenic composition as disclosed herein in the manufacture of a medicament for the method as disclosed herein.

[00309] In some embodiments, the protective immunological response induced in the subject after administration of a vaccine and/or immunogenic composition containing a non-human cell adapted Zika virus of the present disclosure is greater than the immunological response induced in a corresponding subject administered a vaccine and/or immunogenic composition containing a Zika virus that is not adapted for non-human cell growth and/or comprises a different non-human cell adaptation mutation. In some embodiments, the protective immunological response induced in the subject after administration of the vaccine and/or immunogenic composition containing a non-human cell adapted Zika virus of the present disclosure is at least about 5%, at least about 10%, at least about 15%,at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% greater than the immunological response induced in a corresponding subject administered a vaccine and/or immunogenic composition containing a Zika virus that is not adapted for non-human cell growth and/or comprises a different non-human cell adaptation mutation. Methods of measuring protective immunological responses are generally known to one of ordinary skill in the art.

[00310] In some embodiments, administration of a vaccine and/or immunogenic composition containing a non-human cell adapted Zika virus of the present disclosure induces generation of neutralizing antibodies to Zika virus in the subject. In some embodiments, administration of a vaccine and/or immunogenic composition containing a non-human cell adapted Zika virus of the present disclosure induces generation of neutralizing antibodies to Zika virus in the subject in an amount that is greater than the amount of neutralizing antibodies induced in a corresponding subject administered a vaccine and/or immunogenic composition containing a Zika virus that is not adapted for non-human cell growth and/or comprises a different non-human cell adaptation mutation. In some embodiments, administration of a vaccine and/or immunogenic composition

containing a non-human cell adapted Zika virus of the present disclosure induces generation of neutralizing antibodies to Zika virus in the subject in an amount that is at least about 5%, at least about 10%, at least about 15%,at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% greater than the than the amount of neutralizing antibodies induced in a corresponding subject administered a vaccine and/or immunogenic composition containing a Zika virus that is not adapted for non-human cell growth and/or comprises a different non-human cell adaptation mutation. In some embodiments, administration of a vaccine and/or immunogenic composition containing a non-human cell adapted Zika virus of the present disclosure induces generation of neutralizing antibodies to Zika virus in the subject in an amount that is at least about 1-fold, at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 6-fold, at least about 7-fold, at least about 8-fold, at least about 9-fold, at least about 10-fold, at least about 100-fold, or at least about 1000-fold greater than the than the amount of neutralizing antibodies induced in a corresponding subject administered a vaccine and/or immunogenic composition containing a Zika virus that is not adapted for non-human cell growth and/or comprises a different non-human cell adaptation mutation. Methods of measuring neutralizing antibodies in a subject are generally known to one of ordinary skill in the art.

[00311] Preferably, the therapeutically effective amount or immunogenic amount is sufficient to bring about treatment or prevention of disease symptoms. A suitable dosage of about 2µg, about 5µg or about 10µg, in particular about 10µg,

[00312] The present disclosure will be more fully understood by reference to the following Examples. They should not, however, be construed as limiting any aspect or scope of the present disclosure in any way.

EXAMPLES

[00313] Example 1: Clonal Zika Virus Strain Generation

[00314] This example describes the production of Zika virus (ZIKAV) strains with a known research history.

Materials and Methods

Vero Cell Maintenance

[00315] One vial of WHO Vero 10-87 cells was rapidly thawed in a water bath and directly inoculated into 19mL pre-warmed DMEM (Dulbecco's modified minimal essential medium) containing penicillin-streptomycin, L-glutamine 40mM, and 10% FBS in a T-75cm^2 flask at 36°C+/2°C, at 5% CO_2. Cells were allowed to grow to confluency and subcultured using TryplE. This flask was expanded to two T-185cm^2 flasks, grown to confluency and subcultured to 31 xT-185cm^2 flasks and grown until the cells reached 100% confluency. Cells were harvested by trypsinization, centrifuged at 800 x g for 10 minutes, and resuspended in DMEM containing 10% FBS and 10% DMSO at a concentration of 1.9x10^7 cells/mL. One vial of the Vero cells was rapidly thawed and resuscitated as described above into a T-75cm^2 flask. These were subcultured twice to produce a cell bank in 13 x T-185cm^2 flasks. After trypsinization, the cells were centrifuged at 800 x g and resuspended in freezing media (DMEM containing 10% FBS, and 10% DMSO) at a concentration of 4.68x105 cells/mL. This cell bank was aliquoted into cryovials.

[00316] The Vero cells were grown and maintained in DMEM containing penicillin-streptomycin, L-glutamine and 10% FBS (cDMEM-10%-FBS). TryplExpress was used to maintain and trypsinize cells. Two days before viral adsorption, 6-well plates were seeded with 4-5 x 105 cells/well in 3 mL of cDMEM-10%-FBS or 7 x 105 cells in T-25cm2 flasks in 5 mL cDMEM-10%-FBS, or 1 x 104 cells/well in 96-well plates in 0.1mL cDMEM-10%-FBS. Incubators were monitored daily to maintain indicated temperatures. The Vero cell lines were stored in liquid nitrogen.

Plaque Assay

[00317] Viral titers were determined by plaque titration in freshly confluent monolayers of Vero cells grown in 6-well plates. Frozen aliquots were thawed and ten-fold

dilution series of the aliquots were made in cDMEM-0%-FBS in 96-well plates. The diluted viruses were maintained on ice prior to inoculation of the Vero cell monolayers. At the time of assay, the growth medium was aspirated from the 6-well plate, and 100 µL of each virus dilution was added to the wells. Virus was adsorbed for 60 min at 36°C±2°C, at 5% CO2, with frequent (every 10 min) rocking of the plates to prevent drying of the cell sheets. Following viral adsorption, 4 mL of a first agarose overlay (1X cDMEM-2%-FBS + 0.8% agarose) maintained at 40-41°C was added to each well. The agarose was allowed to solidify for 30 min at room temperature, and the plates were then incubated upside down for 4-6 days at 36°C+/2°C, at 5% CO2. Two mL of a second agarose overlay containing 160 µg/mL of neutral red vital dye was added on day 4. Plaques were visualized on days 5 and 6.

Virus Quantification by TCID50 Assay

[00318] Viral titers were also determined by titration in freshly confluent monolayers of Vero cells grown in 96-well plates. Frozen aliquots were thawed and ten-fold dilution series of the aliquots were made in cDMEM-2%-FBS diluent in 96-well plates. The diluted viruses were maintained on ice prior to inoculation of the Vero cell monolayers. At the time of assay, the growth medium was aspirated from the 96-well plate, and 100 µL of each virus dilution was added to the wells. The plates were incubated for 5 days at 36°C+/2°C, at 5% CO2. The 50% Tissue Culture Infective Dose (TCID50) titer was calculated using the Reed/Muench calculator.

Test Articles

[00319] Zika virus strain PRVABC59 (one 0.5 mL vial on dry ice) was received from the Centers for Disease Control and Prevention (CDC) Zika virus identification was confirmed through RT-PCR. The strain tested negative for Alphavirus and mycoplasma contamination by PCR. This information is summarized in Table 1.

Table 1: PRVABC59 strain information

Strain	Isolation Information	Patient information	Prep info	Analyses	PFU
PRVABC59 (Asian)	Human serum; travel to Puerto Rico in 2015	None provided	Passage: Vero(2)C6/36(1) Prep: 29Jan2016 Host: C6/36	▪ Sequencing by ion torrent: gene accession #KU501215 ▪ PFU by plaque assay ▪ Identity by RT-PCR ▪ (-) For alphaviruses by PCR ▪ (-) for mycoplasma by ATCC and ABM PCR	6.7 log pfu/mL

Sequencing

[00320] A QIAampViral RNA Mini Spin kit was used to extract RNA from stabilized virus harvests of each isolate according to manufacturer protocols. Extracted RNA from each isolate was used to create and amplify 6 cDNA fragments encompassing the entire Zika viral genome. Amplified cDNA fragments were analyzed for size and purity on a 1% Agarose/TBE gel and subsequently gel purified using a Qiagen Quick Gel Extraction Kit. An ABI 3130XL Genetic Analyzer sequencer was used to conduct automatic sequencing reactions. Lasergene SeqMan software was used to analyze sequencing data.

Results

[00321] A ZIKAV strain with a known research history that was relevant to the current ZIKAV outbreak in the America's was sought. For this reason, ZIKAV strain PRVABC59 was chosen. To generate a well-characterized virus adapted for growth in Vero cells, the ZIKAV PRVABC59 was first amplified in Vero cells (P1).

[00322] Flasks of Vero cells (T-175cm2), 100% confluent, were infected at an MOI of 0.01 in 4mL of cDMEM-0%-FBS. Virus was adsorbed to the monolayer for 60 minutes at 36°C±2°C, at 5% CO2, then 20 mL of cDMEM-0%-FBS was applied for viral amplification at 36°C±2°C, at 5% CO2. The cell layer was monitored daily for cytopathic effect (CPE) following inoculation (FIG. 1). The supernatant was harvested after 96 hours

by collecting the media and clarifying by centrifugation (600 x g, 4°C, 10 min). The harvest was stabilized by adding trehalose to a final concentration of 18% w/v. The bulk was aliquoted into 0.5mL cryovials and stored at -80 °C.

[00323] The stabilized P1 harvest was analyzed for the presence of infectious virus on Vero cell monolayers by a TCID50 assay. Growth kinetics were monitored by taking daily aliquots beginning on hour 0. Peak titer was reached by hour 72 (FIG. 2).

[00324] P1 material was plaque-purified by titrating the harvest from day 3 on 6-well monolayers of Vero cells. Plaques were visualized on day 6, and 10 plaques to be isolated were identified by drawing a circle around a distinct and separate plaque on the bottom of the plastic plate. Plaques were picked by extracting the plug of agarose using a sterile wide bore pipette while scraping the bottom of the well and rinsing with cDMEM-10%-FBS. The agarose plug was added to 0.5 mL of cDMEM-10%-FBS, vortexed, labeled as PRVABC59 P2a-j and placed in an incubator overnight at 36°C±2°C, at 5% CO2.

[00325] Three plaques (PRVABC59 P2a-c) were carried forward for additional purification. Each isolate was plated neat in duplicate onto a fresh 6-well monolayer of Vero cells. This P2/P3 transition was plaque purified, and labeled PRVABC59 P3a-j.

[00326] Six plaques (PRVABC59 P3a-f) were carried forward for a final round of purification. Each isolate was plated neat in duplicate onto a fresh 6-well monolayer of Vero cells. This P3/P4 transition was plaque purified, and labeled PRVABC59 P4a-j.

[00327] Six plaques (PRVABC59 P4a-f) from the P4 plaque purification were blind passaged on monolayers of Vero cells in T-25 cm2 flasks. Each plaque pick was diluted in 2 mL cDMEM-0%-FBS – 1 mL was adsorbed for 1 hour at 36°C±2°C, at 5% CO2; the other 1 mL was stabilized with trehalose (18% v/v final) and stored at <-60°C. Following virus adsorption, cDMEM-0%-FBS was added to each flask and allowed to grow at 36°C±2°C, at 5% CO2 for 4 days. Virus supernatants were harvested, clarified by centrifugation (600 x g, 4C, 10 min), stabilized in 18% trehalose and aliquoted and stored at <-60°C. This P5 seed was tested by TCID50 for Zika virus potency (FIG. 3).

[00328] Confluent monolayers of T-175cm2 flasks of Vero cells were infected with each of the six clones of PRVABC59 (P5a-f) at an MOI of 0.01 in 4mL cDMEM-0%-FBS. The virus was allowed to adsorb for 60 minutes at 36°C+/2°C, at 5% CO2, after which 20

mL of cDMEM-0%-FBS was added to each flask and allowed to grow at 36°C+/2°C, at 5% CO2. Vero cell monolayer health and CPE was monitored daily. Virus was harvested on days 3 and 5 as indicated (FIG. 4). The P6 strain harvests from days 3 and 5 were pooled, stabilized with 18% trehalose, aliquoted and stored <-60°C.

[00329] Each of the six clones of PRVABC59 (P6a-f) were tested for Zika virus in vitro potency (FIG. 5). The potency was determined by two different methods, TCID50 and plaque titration. The TCID50 was calculated by visual inspection of CPE (microscope) and by measuring the difference in absorbance (A560-A420) of the wells displaying CPE (yellow in color) compared with red (no CPE). The plates were read on a plate reader, and applied to the same calculator as the microscopically read-plates (absorbance). The values in TCID50 between the two scoring techniques are quite similar, while the values obtained by plaque titration are lower.

[00330] A summary of the generation of the P6 virus and characterization is shown in Table 2 below.

Table 2: Summary of virus passage and characterization for the generation of clonal ZIKAV strains

Passage	Seed production/purification	Characterization
P1	Virus amplification in Vero	TCID50 titer
P2	Amplify P1 by plaque titration	plaque purification
P3	Pick and passage plaques from P2 plaque assay	plaque purification
P4	Pick and passage plaques from P3 plaque assay	plaque purification
P5	Amplify P4 plaques (a-f)	TCID50 titer
P6	Amplify P5 (a-f) virus	TCID50 titer, plaque phenotype, genotype, growth kinetics

[00331] An isolated Zika virus clone that closely resembled the envelope glycoprotein sequence of the original isolate was sought, since the envelope protein of flaviviruses is the dominant immunogenic portion of the virus. PRVABC59 clones P6a, P6c, P6d and P6f contained a G→T mutation at nucleotide 990 in the envelope region (G990T), resulting in an amino acid mutation of Val→Leu at envelope residue 330, whereas the envelope gene of PRVABC59 clones P6b and P6e were identical relative to the reference strain (GenBank ref KU501215.1) (Table 3 and FIG. 6).

Table 3: Sequencing of PRVABC59 P6 clones

Envelope sequencing (reference gene from PRVABC59; accession #KU501215)				
Strain	**Nucleotide**	**Amino Acid**	**Mutation**	**Comments**
PRVABC59 P6a	Env-990: G→T	Env-330: Val330→Leu	**Val/Leu**	Mutation in 3 of 4 reads.
PRVABC59 P6b	Env-1404: T→G silent	Wild type	Wild type	Wild type relative to reference.
PRVABC59 P6c	Env-990: G→T	Env-330: Val330→Leu	**Val/Leu**	Mutation in 3 of 4 reads.
PRVABC59 P6d	Env-990: G→T	Env-330: Val330→Leu	**Val/Leu**	Mutation in 2 of 2 reads.
PRVABC59 P6e	Wild type	Wild type	Wild type	Wild type relative to reference.
PRVABC59 P6f	Env-990: G→T	Env-330: Val330→Leu	**Val/Leu**	Mutation in 2 of 2 reads. 190 bp not sequenced (aa 421 – 484).
Full genome sequencing (reference gene from PRVABC59;accession #KU501215)				
Strain	**Nucleotide**	**Amino Acid**	**Mutation**	**Comments**
PRVABC59 P6b	Env-1404 T→G	Wild-type	Silent	Mutation in 2 of 2 reads
	NS1-292 T→G	NS1-98 Trp98→Gly	**Trp/Gly**	Mutation in 2 of 2 reads
PRVABC59 P6e	NS1-292 T→G	NS1-98 Trp98→Gly	**Trp/Gly**	Mutation in 2 of 2 reads

[00332] The two clones lacking mutations in the envelope sequence were then subjected to full genome sequencing. Sequencing results are summarized in Table 3 above. Sequence analysis revealed a T→G substitution at nucleotide 292 in the NS1 region for both clones, resulting in a Trp→Gly mutation at NS1 residue 98. This mutation was also later confirmed through deep sequencing. The NS1 W98G mutation is located in the intertwined loop of the wing domain of ZIKAV NS1, which has been implicated in membrane association, interaction with envelope protein and potentially hexameric NS1 formation. While other tryptophan residues (W115, W118), are highly conserved across flaviviruses, W98 is not (FIG. 7). Interestingly, however, 100% conservation of the W98 residue is observed across 11 different ZIKAV strains, including those from the African and Asian lineages. The identified mutations in each strain are summarized in Table 4.

Table 4: Summary of mutations identified in PRVABC59 P6 clones

Mutations identified in envelope		
Clone	**Nucleotide**	**Amino Acid**
P6a	G990T	V330L
P6b	T1404G	(silent)
P6c	G990T	V330L
P6d	G990T	V330L
P6e	none	none
P6f	G990T	V330L
Additional mutations identified in genome		
Clone	**Nucleotide**	**Amino Acid**
P6b	NS1-T292G	NS1-W98G
P6e	NS1-T292G	NS1-W98G
Ref sequence: KU501215.1 (PRVABC59)		

[00333] Phenotypic analysis of the ZIKAV PRVABC59 P6 stocks was conducted to characterize the ZIKAV clones. As illustrated in FIG. 8 and quantified in FIG. 9, each clonal isolate consisted of a relatively homogeneous population of large-sized plaques as compared to the P1 virus which had a mixed population of large and small plaques. These data suggest the successful isolation of single ZIKAV clones.

[00334] Next, growth kinetics analyses in Vero cells of the ZIKAV PRVABC59 P6 clones were analyzed. Vero cells were infected with 0.01 TCID50/cell of each ZIKAV P6 clones in serum free growth medium. Viral supernatant samples were taken daily and simultaneously assayed for infectious titer by TCID50 assay. For all P6 clones, peak titer occurred between day 3 and 4 (~9.0 log10 TCID50/mL). There was no significant difference in growth kinetics of the various P6 clones (FIG. 10).

[00335] Taken together, the results indicate that a Zika virus seed was successfully generated. This seed selection required understanding of growth history, kinetics, yield, genotype, and phenotype of the virus. Importantly, clonal isolation of the Zika virus strains allowed for the successful purification of the virus away from contaminating agents (e.g., adventitious agents that may be in the parental human isolate). Interestingly, three sequential plaque purifications succeeded in quickly selecting Vero-cell adapted virus (strains P6a-f), where these strains were able to replicate well in serum-free Vero cell

cultures, with strain P6a, c, d, and f harboring a mutation in the viral envelope protein, while strains p6b and p6e obtained a mutation in the viral NS1 protein (with no modification to the viral envelope). Additionally, the Vero-adapted strains enabled efficient and reproducible growth and manufacture of subsequent viral passages propagated from these strains. Without wishing to be bound by theory, the Env-V330L mutation observed in strains P6a, c, d, and f may potentially be a result of in vitro adaptation, as a mutation at Env 330 was also observed upon passaging in Vero cells (Weger-Lucarelli et al. 2017. Journal of Virology). Because the envelope protein is the dominant immunogenic epitope of Zika virus, strains containing a Vero adaptive mutation in Env may negatively impact vaccine immunogenicity. Without wishing to be bound by theory, the adaptation mutation in protein NS1 appears not only to enhance viral replication, but may also reduce or otherwise inhibit the occurrence of undesirable mutations, such as in the envelope protein E (Env) of the Zika virus. In addition, NS1 may be known to bind to the Envelope protein during the life cycle of the virus. This mutation (NS1 W98G) may be implicated in changing the ability of the NS1 to associate, and possibly co-purify, with the virus during downstream processing. NS1 is also known to be immunogenic, and could be implicated in the immune response to the vaccine.

Example 2: Preclinical immunogenicity and efficacy of a purified inactivated Zika virus vaccine (PIZV) derived from the P6b and P6e strains

[00336] The following example describes the preclinical immunogenicity and efficacy in CD1 and AG129 mice of an inactivated Zika virus vaccine (PIZV) derived from the P6b and P6e strains. As described in Example 1, six clones were generated from the epidemically relevant PRVABC59 strain, and two (P6b and P6e) were chosen for further preclinical immunogenicity and efficacy studies.

Materials and Methods

Purification, inactivation and formulation of a Zika virus vaccine

[00337] A lot of inactivated ZIKAV vaccine, suitable for use in preclinical immunogenicity and efficacy studies, was generated and characterized. Virus was amplified from the P6b and P6e strains by infecting flasks of confluent Vero cells at a MOI of 0.01. Virus was adsorbed for 1 hour at 36°C ± 2°C / 5% CO2. Following adsorption, 20 mL of cDMEM-0%-FBS was added to each flask, and incubated at 36°C ± 2°C / 5% CO2 for five

days. Cell supernatants were harvested on day 3 and 5 post-infection, and cell debris was clarified by centrifugation.

[00338] For each isolate, clarified supernatants were pooled, stabilized in DMEM containing 18% trehalose and stored at <-60°C. Pooled, clarified virus supernatants were thawed in a 37°C water bath and treated with benzonase overnight at 4°C. Following benzonase treatment, each sample was applied to a Sartorius PP3 depth filter. Following depth filtration, each sample was applied to a Centricon Plus-70 tangential flow filtration (TFF) device. Retentate was buffer exchanged, diluted, and applied to a Sartorius SartobindQ IEXNano. Each sample was applied to a second Sartorius SartobindQ IEXNano and eluted using a 3 step-elution process with 250 mM, 500 mM, and 750 mM NaCl. Following MonoQ chromatography and dilution, each 250 mM eluate was applied to a Centricon Plus-70 cross flow filtration (CFF) device for buffer exchange, diluted to 35 mL with PBS, and stored at 2-8°C.

[00339] For formalin inactivation, freshly prepared 1% formaldehyde was added dropwise to each purified sample with gentle swirling to obtain a final formaldehyde concentration of 0.02%.Samples were incubated at room temperature (~22°C) for 14 days with daily inversion. Formaldehyde was neutralized with sodium metabisulfite for 15' at room temperature before being applied to a Centricon Plus-70 tangential flow filtration (TFF) device. Buffer exchange was performed four times by the addition of 50 mL Drug Substance Buffer (10 mM NaH_2PO_4 , 50 mM NaCl, 6% sucrose, pH 7.4) . Each sample was then diluted to 15 mL with Drug Substance Buffer, sterilized using a 0.2m syringe filter, aliquoted into sterile stoppered glass vials (0.5 mL per vial) and frozen at <-60°C.

[00340] Virus inactivation was confirmed by TCID50 assay and double infectivity assay. Briefly drug substance sample was applied to C6/36 cells and allowed to amplify for 6 days. Supernatant from C6/36 cells was applied to Vero cells and CPE was monitored for 8 days. For drug product formulation, vials of PIZV drug substance were thawed, pooled according to sample type, and diluted to 1 μg/mL or 10 μg/mL in PBS with or without Alhydrogel (Brenntag ; 0.5 mg/mL final, 0.050 mg/dose) and incubated overnight at 2-8°C with gentle agitation. The resulting drug product lots were then aliquoted into sterile stoppered glass vials and stored at 2-8°C until use. FIG. 11 provides a summary of the steps used to prepare drug product.

Mouse immunization and challenge

[00341] For the immunogenicity study, six-week old male and female Swiss-ICR (CD-1) mice were divided into 6 groups (n = 10/group). On Day 0, mice in groups 1-5 were inoculated with 0.1 mL of vaccine by the intramuscular (i.m.) route (2 x 0.05 mL injections). Mice in group 6 were inoculated with PBS as a placebo control. Mice were boosted on day 28 and 56 using the same dosage and vaccine type as day 0. Blood samples were collected on day -1 (pre-immune), day 27 (prime), day 42 (boost 1) and day 70 (boost 2).

[00342] For the immunogenicity and efficacy study, four-week old male and female AG129 mice were divided into 7 groups (n = 5/group). On Day 0, mice in groups 1-6 were inoculated with 0.1 mL of vaccine by the intramuscular (i.m.) route (2 x 0.05 mL injections). Mice in group 7 were inoculated with PBS as a placebo control. Mice were boosted on day 28 using the same dosage and vaccine type as on day 0. Blood samples were collected from the tail vein on day -1 (pre-immune), day 27 (prime) and day 55 (boost). At the time of euthanization, mice were bled via cardiac puncture under deep anesthesia with isofluorane (terminal). On day 56, mice were intraperitoneally challenged with 104 plaque forming units (PFU) of ZIKAV PRVABC59.

Serum transfer

[00343] Serum was collected from PIZV-vaccinated and challenged AG129 mice, and were frozen after pooling (groups 1, 2, 4, and 5 of Table 6). The serum pool was thawed, and the test articles were generated by three-fold dilutions of the serum pool in PBS. A placebo was generated using 3-fold dilutions of AG129 normal mouse serum in PBS.

[00344] The test articles were administered as 0.1 mL intraperitoneal injections into AG129 mice (an equivalent volume of the placebo article was administered to control mice). Animals were then challenged intraperitoneally with 104 plaque forming units of Zika virus strain PRVABC59 in 100µL.

[00345] Allowable blood volume by weight was collected as whole blood by tail bleeding from ten mice on day -11 (pre-immunization). Whole blood was collected from each mouse on day 1 (primary, circulating Nab) and day 4 (viremia) by tail bleeding.

Terminal bleeding after lethal challenge was performed by heart puncture under deep anesthesia for larger volume before euthanization by cervical dislocation. Blood samples were collected in microtainer SST serum separation gel tubes and allowed to clot for at least 30 min before separation of serum by centrifugation (10,000 x g for 2 min) and frozen at -80°C.

Plaque reduction neutralization test

[00346] Neutralizing antibody titers were determined by a plaque reduction neutralization test (PRNT) as described previously (See e.g., Osorio et al. Lancet Infect Dis. 2014 Sep;14(9):830-8).

Reporter virus particle (RVP) neutralization assay

[00347] Neutralizing antibody titers were analyzed by titration of serum samples with a constant amount of Zika RVPs in Vero cells grown in 96-well plates. RVPs contained the prME proteins of Zika (strain SPH2012) and a Dengue-based Renilla luciferase reporter. Briefly, sera were heat inactivated at 56°C for 30 min, diluted, and then incubated at 37°C with RVPs. The serum/RVP mixture was then mixed with Vero cells and incubated for 72 hours at 37°C ± 2°C/ 5% CO2 before detection with luciferase substrate. Data was analyzed using JMP11 non-linear 4 parameter analysis, normalized to a positive tracking control and effective dose 50% (EC50) was reported.

[00348] Unless indicated to the contrary, all additional experimental methods were carried out as described in Example 1 above.

Results

[00349] To assess the immunogenicity of the PIZV candidates in 6 week old male and female CD-1 mice, groups of CD-1 mice (N=10/group) were immunized by the i.m. route with either a 0.1 µg (+ alum), 1.0 µg (+ alum) dose of a vaccine derived from either ZIKAV PRVABC69 P6b or P6e virus strains. To assess the need for adjuvant, a group of animals was vaccinated with 0.1 µg of vaccine derived from P6e and lacking alum adjuvant. Vaccinations occurred on days 0, 28, and 56, with group 6 receiving PBS as a placebo control (FIG. 12A and Table 5).

Table 5: PIZV formulations and challenges in CD-1 mice

Group	Strain	Dose (µg)	Alum (µg)	N
1	P6b	0.1	0.50	10
2	P6b	1.0	0.50	10
3	P6e	0.1	0.50	10
4	P6e	1.0	0.50	10
5	P6e	0.1	-	10
6	Placebo (PBS)	-	-	10

[00350] Following vaccination, serum samples collected after primary (day 27), secondary (day 40) and tertiary (day 70) immunizations were tested for ZIKAV-specific neutralizing antibodies by RVP neutralization assay (FIG. 12B). Twenty-seven days after receiving the first dose, a slight neutralizing antibody response was observed in mice vaccinated with PIZV derived from either clone containing alum, as compared to the PBS placebo control group. Importantly, this response increased significantly upon a second immunization (day 40), but was not additionally enhanced upon immunization with a third dose (day 70). No neutralizing antibody response was observed in mice vaccinated with non-adjuvanted vaccine (FIG. 12B).

[00351] To assess the immunogenicity and protective efficacy of the PIZV candidates, groups of 4 week old AG129 mice (n=5/group) were immunized by the i.m. route with either a 0.1 µg dose (+ alum), 1.0 µg dose (+ alum) or 0.1 µg dose (- alum) of a vaccine derived from either the ZIKAV PRVABC59 P6b or P6e stocks on days 1 and 28 (FIG. 13A and Table 6).

Table 6: PIZV formulations and challenges in AG129 mice

Group	Sex	Strain	Dose (µg)	Alum (µg)	N
1	F	P6b	0.1	0.50	5
2	F	P6b	1.0	0.50	5
3	F	P6b	0.1	-	5
4	M	P6e	0.1	0.50	5
5	M	P6e	1.0	0.50	5
6	M	P6e	0.1	-	5
7	M	Placebo (PBS)	-	-	5

[00352] Following vaccination, vaccinated and control mice were intraperitoneally challenged at day 56 with 104 PFU of ZIKAV PRVABC59 (low passage). Serum samples collected after primary (D27) and secondary (D55) immunizations were tested for ZIKAV-

specific neutralizing antibody response (FIG. 13B and Table 7). Only groups receiving the high dose of alum-adjuvanted vaccine (groups 2 and 5) elicited a neutralizing antibody response after a single immunization, which increased dramatically after boosting. In contrast, groups receiving either the low or high dose of alum-adjuvanted vaccine produced a high neutralizing antibody response after a second dose. Upon receiving two doses of vaccine, there was no statistical difference between groups of mice receiving alum-adjuvanted vaccine, regardless of the dosage or the derivation from the P6 clone.

Table 7: ZIKAV-specific neutralizing antibody response

		Serum neutralizing antibody titers			
		D27 (prime)		D55 (boost)	
Group	**Formulation**	**GMT**	**% sc**	**GMT**	**% sc**
1	P6b 0.1 µg + alum	<20	40	1280	100
2	P6b 1.0 µg + alum	135	80	2229	100
3	P6b 0.1 µg - alum	<20	0	<20	0
4	P6e 0.1 µg + alum	<20	20	640	100
5	P6e 1.0 µg + alum	30	100	905	100
6	P6e 0.1 µg - alum	<20	0	<20	20
7	PBS	<20	0	<20	0

[00353] All groups were also monitored for mortality, morbidity and weight loss for 21 days post challenge. Viremia following challenge was detected and quantitated by plaque titration. Mice vaccinated with a low or high dose of PIZV candidates formulated with alum (groups 1, 2, 4 and 5) were fully protected from lethal ZIKAV challenge, as assessed by the plaque reduction neutralization test (PRNT) assay, as well as a comparable secondary neutralization assay (Table 8). No weight loss or clinical signs of illness were observed in vaccinated mice, none had detectable infectious viremia three days post challenge, and all mice vaccinated with either low or high dose antigen + alum adjuvant survived to 21 days post-challenge (FIGS. 14-16). In contrast, challenge of all naïve mice resulted in high viremia on day 2 post challenge and morbidity/mortality between day 10 and 18 post challenge (median survival = D13). Additionally, challenge of mice vaccinated with a non-alum-adjuvanted low dose vaccine derived from strain P6b resulted in high

viremia on day 2 post challenge and a median survival day similar to the placebo control group, while mice vaccinated with a non-alum-adjuvanted low dose derived from clone e remained partially protected with a median survival of 19 days. These results indicate immunization is more effective with alum, secondary immunization may be a requirement, and that low dose was as effective as high dose.

Table 8: Serum neutralizing antibody titers

Pool	Serum neutralizing antibody titers	
	Terminal (post challenge)	
	$PRNT_{50}$	Secondary assay
Alum (1,2,4,5)	10240	20480
No alum (3,6)	2560	2560
PBS (7)	1280	1280

[00354] Additionally, the presence of NS1 in the vaccine drug substance (DS) produced from whole inactivated P7b and P7e virus (one additional passage from the P6b and P6e strains, respectively) was tested. A sandwich ELISA was performed using plates pre-coated with a monoclonal antibody reactive to both Asian and African lineages of Zika virus NS1, but non-cross-reactive to Dengue NS1. Duplicate 2-, 4-, 8-, 16-, and 32-fold dilutions of DS were prepared, and were compared to a standard curve using recombinant purified NS1 in duplicate at a concentration of 0-8 ng/mL. Duplicate dilutions of DS buffer alone were prepared as negative controls. Bound NS1 was detected with anti-NS1 HRP-conjugate, and absorbance (A450-A630) of the wells with DS buffer alone was subtracted from the absorbance measured in the wells containing the matching DS samples. Results of the sandwich ELISA are shown in Table 9 below. Interestingly, NS1 was observed to co-purify with the vaccine drug substance preparations, suggesting that viral NS1 may be an immunogenic component of the whole inactivated virus vaccine.

Table 9: NS1 ELISA

Strain in vaccine preparation	Sample OD	Predicted log ng/mL	Std Error	Lower 95%	Upper 95%	Dilution Factor	Predicted concentration (ng/mL)
P7b	3.61	0.951	0.018	0.915	0.986	32	~285
P7e	3.79	0.980	0.023	0.935	1.024	32	~306

[00355] The threshold of neutralizing antibody (Nab) needed to confer protection from wild-type Zika virus challenge after passive transfer of antibodies was next tested. (Tables 10A and B).

Table 10A: design of passive transfer study in AG129 mice

Group	Test Article	Serum dilution	Predicted Nab titer before IP
1	100 µL	1/3	6827 / 3.83
2	100 µL	1/9	2276 / 3.36
3	100 µL	1/27	759 / 2.88
4	100 µL	1/81	253 / 2.40
5	100 µL	1/243	84 / 1.93
6	100 µL	1/729	28 / 1.45
7	100 µL	1/2187	9 / 0.97
8	100 µL	PBS	-

Table 10B: Timing of passive transfer study in AG129 mice

Description	Study Day
Passive transfer	Day 0
Primary Bleed (AM)	Day 1
Challenge (PM)	Day 1
Viremia Bleed	Day 4
Terminal Bleed	Day 29 for survivors

[00356] Pooled serum from vaccinated and challenged AG129 mice was serially diluted 3-fold in PBS and intraperitoneally injected into 7 groups (N=5/group) of 5-6 week old AG129 mice. Pre-immune AG129 mouse serum was used as placebo control (group 8). Following passive transfer (~16-19 hours later), whole blood was collected and serum was separated by centrifugation from each mouse prior to virus challenge for determination of circulating neutralizing antibody titer (FIG. 17). Just prior to virus challenge, groups of mice (designated groups 1, 2, 3, 4, 5, 6, 7, 8) had mean log10 neutralizing antibody titers of 2.69, 2.26, 1.72, 1.30, <1.30, <1.30, <1.30, <1.30, respectively.

[00357] Twenty four hours following passive transfer of ZIKV nAbs, mice were intraperitoneally challenged with 104 pfu of ZIKV PRVABC59. Following challenge, animals were weighed daily and monitored 1-3 times a day for 28 days for signs of illness. A clinical score was given to each animal based on the symptoms (Table 11). Animals that were moribund and/or showed clear neurological signs (clinical score ≥2) were humanely euthanized and counted as non-survivors.

Table 11: Description of clinical scores given while monitoring for morbidity and mortality

Score	Description
0	Normal appearance and behavior
1	Slightly ruffled fur and/or general loss of condition
2	Increases in above behavior/appearance, breathing changes, twitching, anti-social behavior
3	First signs of neuropathy – Severely hunched posture, partial paralysis (immobility, unsteady gait, flaccid hind legs, severe twitching), or full paralysis
4	Found dead without showing signs of score of 2 or 3 first

[00358] Signs of disease began appearing nine days after challenge in the control group (group 8) and groups 5-7, with a corresponding loss in weight (FIG. 18). Whole blood was collected and serum was separated by centrifugation from each animal three days post challenge. Serum samples were analyzed for the presence of infectious ZIKV using a plaque titration assay (FIG. 19). The mean infectious titer (log10 pfu/mL) for mice in groups 1-8 were: 1.66, 2.74, 4.70, 4.92, 7.24, 7.54, 7.54 and 7.46, respectively. Importantly, mice in groups 1-4 with detectable levels of ZIKV neutralizing antibodies (≥1.30 log10) had statistically significant lower levels (102.5- to 106.0- fold lower titers) of viremia ($p = 0.0001, 0.0003, 0.0007$ and 0.0374) than control mice. These results suggested that detectable levels of ZIKV neutralizing antibodies (≥1.30 log10) reduced viremia in a dose-dependent manner.

[00359] The median survival day of mice in groups 1-8 were: not determined, day 17, day 17, day 13, day 11, day 11, day 11, and day 10, respectively (FIG. 20). Importantly, the survival curves for groups of mice with detectable ZIKV neutralizing antibody titers (groups 1-4) were statistically different compared to the control group (group 8) ($p = 0.0019, 0.0019, 0.0019, 0.0153$, respectively). These results suggested that detectable levels (≥1.30 log10) of ZIKV neutralizing antibodies delayed onset of disease in a dose-dependent manner.

[00360] Finally, the ZIKV neutralizing antibody titer of each animal was graphed against its corresponding viremia titer and linear regression analysis was performed. A highly inversely correlated relationship between ZIKV neutralizing antibody titers and viremia levels at day 3 post-challenge was observed (FIG. 21). A summary of the results from the passive transfer studies is shown in Table 12 below.

Table 12: Summary of passive transfer results

Group	Serum dilution	Circulating ZIKV nAb GMT	Viremia (D3) log10 pfu/mL	% survival (D28)	Median survival day
1	1/3	2.69 ± 0.17	1.66 ± 0.62	20	24
2	1/9	2.26 ± 0.13	2.73 ± 0.68	0	17
3	127	1.72 ± 0.16	4.69 ± 0.77	0	17
4	1/81	1.30 ± 0.16	4.94 ± 1.29	0	13
5	1/243	<1.30	7.25 ± 0.10	0	11
6	1/729	<1.30	7.54 ± 0.31	0	11
7	1/2187	<1.30	7.52 ± 0.39	0	11
8	PBS	<1.30	7.47 ± 0.37	0	10

[00361] While no groups of mice receiving ZIKAV neutralizing antibodies were fully protected from lethal ZIKAV challenge in this experiment, reduced viremia levels and delayed onset of disease in a dose-dependent manner among the groups of mice with detectable levels of circulating ZIKAV neutralizing antibody titers was demonstrated.

[00362] Taken together, preclinical data from both CD-1 and AG129 mouse studies indicate that a PIZV derived from separate and well-characterized viral clones are immunogenic and able to provide protection against challenge with wild-type ZIKAV. Importantly, a low and high vaccine dose elicited a similar neutralizing antibody response after two doses, and provided similar levels of protection against lethal ZIKAV challenge. Interestingly, mice vaccinated with an unadjuvanted PIZV candidate also showed partial protection from ZIKAV challenge. Vaccine antisera significantly diminished viremia in passively immunized AG129 mice, and prolonged survival against lethal ZIKAV challenge. These results also demonstrate that the well-characterized PIZV candidates were highly efficacious against ZIKAV infection in the highly ZIKAV-susceptible AG129 mouse model.

[00363] Additionally, it was found that the sequence of a PRVABC59 (from PRVABC59 P6e) at passage 7 was genetically identical to that of passage 6. This was surprising given that flaviviruses are generally regarded as genetically labile. PRVABC59 P6e was selected as the master virus seed due in part to its genetic stability over 7 passages. Without wishing to be bound by theory, it is believed that this enhanced genetic stability

may be due to the single amino acid substitution (W98G) in the wing domain of NS1, as this was the only mutation observed in the Vero cell-adapted PRVABC59 P6 genome. Additionally, genetic stability and homogeneity is advantageous in that it reduces variability and increases reproducible production of subsequent strains that may be used for vaccine formulation.

Example 3: Preclinical assessment of the phenotype of the P6a and P6e strains

Materials and Methods

[00364] AG129 mice (lacking interferon α/β and γ receptors) are susceptible to ZIKV infection and disease, including severe pathologies in the brain. 14-week-old AG129 mice were intraperitoneally infected with with 10^4 and 10^3 pfu of the ZIKV passage 6 clones a (P6a) and e (P6e)..

[00365] Mice were weighed and monitored daily (up to 28 days) for clinical signs of illness (weight loss, ruffled fur, hunched posture, lethargy, limb weakness, partial/full paralysis). Additionally, analysis of viremia was performed by plaque titration of serum samples collected three days post-challenge as described in Example 1.

Results

[00366] Infection with P6e resulted in 100% mortality (median survival time = 12.5 days), while infection with P6a resulted in only 33% mortality (median survival time = undetermined) (Figure 22). In agreement with this, preMVS P6e infected mice showed greater weight loss as compared to PRVABC59 P6a infected mice (3). No statistical difference was found in mean group viremia levels between groups of mice infected with PRVABC59 P6a or P6e (Figure 24). These data suggest that growth kinetics alone may not be a key determinant (since both strains produced similar viremia, and similar peak titers in vitro) and that a characteristic of the Envelope protein could be important for virulence (of a wildtype strain) and immunogenicity (of an inactivated candidate).

Example 4: Clinical immunogenicity and efficacy of a purified inactivated Zika virus vaccine (PIZV) derived from P6e strains

Sample preparation:

[00367] Four Purified Inactivated Zika Vaccine (PIZV) lots (Tox lots 1-4) were manufactured by growth in Vero cells as described above. Supernatants from 4 daily

harvests (each daily harvest 1000mL daily, totaling about 4000 mL) were purified by filtration and chromatography, concentrated and inactivated by addition of formalin to a final concentration of 0.01%. Inactivation was allowed to proceed for 10 days at 22°C, before the sample was buffer exchanged into Drug Substance Buffer (10 mM NaH_2PO_4, 50 mM NaCl, 6% sucrose, pH 7.4).

[00368] The inactivated Zika virus active agent is no longer able to infect host cells, which can be infected with a Zika virus which has not been inactivated. The inactivation is determined by the following test protocol. In activation is acknowledged in case no plaques are detectable.

Detailed COI (Completeness of Inactivation) protocol:

[00369]

1. First part of the assay: Vero (1 .$4E^{+05}$ cells/mL) and *Aedes aegypti* mosquito C6/36 ($4E^{+05}$ cells/mL) cells were seeded in 96-well plates two days prior to addition of the samples. The Vero cells were cultured in DMEM + 10% final FBS + 2% L-glutamine + 1% penicillin/streptomycin at 37ºC. C636 cells were cultured in DMEM + 10% FBS + 2% L-glutamine + 1% Penicillin/streptomycin + 1% nonessential amino acids at 28ºC.
2. Three independent replicates of the 200 TCID50 control virus (prepared in the virus back titration control test) or the DS samples were diluted (5-fold and 10-fold dilutions) into media containing 2% FBS.
3. The cells in 96-well plates were inoculated with the samples. Prior to the infection of the cell monolayers in the 96-well plates, the sample was vortexed to disrupt any possible aggregation. 100 µL of each dilution was applied to each of 5 wells into two separate 96-well plates containing Vero and C636 cells, respectively.
4. Media alone was included in another well for each cell type as a negative CPE control.
5. Plates were incubated for 6 days at the appropriate temperature for the cell line.
6. Second part of the assay: To allow live virus to be further amplified and visualized by CPE on a permissive cell line, the entire volume of each 96-well supernatant from both Vero and C636 cells was transferred to individual wells of

6-well plates of Vero cells. Inoculation proceeded for 90 minutes with rocking at 15 minutes intervals.

7. Medium containing 2% FBS was added to the wells and plates were incubated for an additional 8 days for subsequent detection of the amplified samples as a function of CPE. The inactivation was considered to be incomplete if any of the replicates of the DS showed CPE at the end of day 8.

7. The presence of live/replicating virions was visualized by the formation of plaques or CPE on susceptible cell monolayers after transfer to the 6-well plate, and incubation for 8 days to allow for viral replication. The % CPE scoring in the 6-well plates at the end of the assay was calculated as follows:

    - Each 6-well plate of Vero cells was examined for CPE by visualization of colorimetric change, followed by confirmation of CPE by inspection under an inverted light microscope.
    - Each 6-well plate represented one of the replicates of the DS dilutions prepared in the 5 and 10-fold dilutions described above (5 wells, plus one well containing media alone).

    Therefore, % CPE for each replicate reflected the number of wells with CPE out of 5 total wells per sample (120 total wells are used per assay). Mean % CPE and standard deviation were calculated based on three replicates of each dilution.

[00370] The amount of the purified inactivated Zika virus can be determined by a Bradford assay (Bradford et al. (1976) Anal. Biochem. 72: 248-254) using defined amounts of recombinant Zika envelope protein to establish the standard curve.

[00371] The purity of the purified Zika virus can be determined by size exclusion chromatography. In the current example, the main peak of the purified Zika virus in the size exclusion chromatography was more than 85% of the total area under the curve in the size exclusion chromatography.

[00372] The investigational vaccine (PIZV) refers to Zika purified formalin-inactivated virus formulated with 200 μg aluminum hydroxide, Al(OH)3, as adjuvant, in phosphate buffered saline solution (PBS). The final liquid formulated product is filled into single-use vials and sealed with tamper-evident seals. The investigational vaccine is

administered IM (intramuscularly) as a 2-dose regimen of 0.5 mL at 2, 5, or 10 μg antigen per dose, 28 days apart.

[00373] Sodium chloride (NaCl) 0.9% solution for injection is being used as placebo. It is supplied in single-use vials. It is a sterile, clear, colorless liquid solution of sodium chloride without preservative designed for parenteral use only. The placebo is administered IM as a 2-dose regimen of 0.5 mL per dose, 28 days apart.

Test methods

[00374] PRNT assay: Neutralizing antibody titers were determined by a plaque reduction neutralization test (PRNT) as described previously (See Protection of Rhesus monkeys against dengue virus challenge after tetravalent live attenuated dengue virus vaccination. J. Infect. Dis. 193, 1658–1665 (2006). Muthumani K, Griffin BD, Agarwal S, et al. In vivo protection against ZIKV infection and pathogenesis through passive antibody transfer and active immunisation with a prMEnv DNA vaccine. NPJ Vaccines 2016; 1: 16021). The Zika strain used for PRNT assay development was PRVABC59.

Immuno Outcome Measures:

Definitions:

[00375] Sero-positivity (PRNT): titers of ≥LOD (Limit of detection)

[00376] Sero-negativity (PRNT): titers of <LOD (Limit of detection)

[00377] Seroconversion (PRNT): Post vaccination titers of ≥LOD in initially seronegative subjects

[00378] LOD (PRNT) = 10

[00379] Assigned value for below LOD = 5

[00380] LLoQ (Lower Limit of Qualification, PRNT) = 26

[00381] Assigned value for below LLoQ (Lower Limit of Qualification) = 13

[00382] Reporter virus particle (RVP) neutralization assay: Neutralizing antibody titers were analyzed by titration of serum samples with a constant amount of Zika RVPs in

Vero cells grown in 96-well plates. RVPs contained the prME proteins of Zika (strain SPH2012) and a Dengue-based Renilla luciferase reporter. Briefly, sera were heat inactivated at 56°C for 30 min, diluted, and then incubated at 37°C with RVPs. The serum/RVP mixture was then mixed with Vero cells and incubated for 72 hours at 37°C ± 2°C/ 5% CO2 before detection with luciferase substrate. Data was analyzed using JMP11 non-linear 4 parameter analysis, normalized to a positive tracking control and effective dose 50% (EC50) was reported.

Study description

[00383] A Phase 1, Randomized, Observer-Blind, Placebo-Controlled, Safety, Immunogenicity, and Dose Ranging Study of Purified Inactivated Zika Virus Vaccine (PIZV) in Flavivirus Naïve and Primed Healthy Adults Aged 18 to 49 Years

[00384] The study design is shown in Figure 25. This study was designed to sequentially enroll flavivirus-naïve and flavivirus-primed healthy adults between the ages of 18 and 49 years. The two sequential cohorts are each comprised of 120 subjects (planned) randomly allocated to one of 4 groups of 30 subjects, to receive either one of three dosages of the PIZV vaccine or saline placebo. The vaccination regimen consists of 2 doses administered 28 days apart. The data in this example only relates to the Flavivirus naïve subjects (n=124), further data with Flavivirus primed subjects are to be expected. This example provides data from a first interim analysis following Day 57 (28 days post-dose 2) for the "flavivirus-naïve cohort". Data from the flavivirus-primed cohort are not part of this interim analysis, as recruitment for this group was still ongoing at the time first interim analysis.

[00385] In summary, subjects were randomized into four study groups, who received two doses of either placebo (saline) or purified inactivated Zika vaccine (PIZV) with a concentration of 2 µg, 5 µg and 10 µg. The study involved intramuscular injection of the vaccine (or placebo) at day 1 and day 29, with blood samples being taken on day -15, 1, 8, 29, 36, 57, 211, 393, 767 of the study. Blood samples on day -15 were used to determine Flavivirus serostatus screening and eligibility screening. Samples on day 1, 29, 57 were for immunogenicity assessment. Safety lab testing was carried out on days 8 and 36. Persistence of immunity will be assessed on day 211, 393 and 767.

[00386] Based on the data from 28 days post dose 2, the purified inactivated Zika virus vaccine (PIZV) was safe and immunogenic in Flavivirus-naïve adults aged between 18-49 yrs.

Primary Objectives

[00387] The primary objective of the study was to describe the safety of two doses of PIZV given 28 days apart and to select a dose level from three different antigen concentrations (2, 5 or 10 µg) for use in subsequent clinical studies. The primary endpoints were: the percentages of subjects experiencing solicited local and systemic adverse events (AEs) during the 7-day period after administration of each dose of PIZV or placebo, and the percentages of subjects experiencing non-serious unsolicited AEs and serious adverse events (SAEs) during the 28-day period after vaccination.

Secondary Objectives

[00388] The secondary objectives were to describe the immune response to the purified inactivated Zika virus vaccine (PIZV) at 28 days post dose 1 and 28 days post dose 2 in flavivirus naïve adults. The secondary endpoints related to these objectives are geometric mean titers (GMTs) of neutralizing anti-ZIKV antibodies, seropositivity rates (SPR) and seroconversion rates (SCR) at the considered timepoints.

[00389] Analysis of the data was performed by a separate set of unblinded statisticians and programmers, who had access to the individual treatment assignments. All personnel involved in the conduct of the trial were blinded to the individual subject treatment assignments. The study team had access to the group level unblinded results only.

Study population:

[00390] A total of 124 subjects were enrolled in the flavivirus-naïve cohort and included in the Safety Set (SS), comprised of all randomized subjects who have received at least one dose of PIZV or placebo. Among those, 118 (95.2% of the SS) were included in the Full Analysis Set (FAS) of randomized subjects who had received at least one dose of

the investigational vaccine (PIZV)/placebo, provided valid serology results at baseline and at least once post-vaccination. One hundred and thirteen (113) subjects (91.1% of the SS) were included in the Per Protocol Set (PPS) of subjects in the FAS who had no major protocol violations relevant for the immunogenicity analysis. The analysis sets are presented in Table 14.

Table 14: Analysis sets

	Number of Subjects (%)				
	Placebo	**2µg PIZV**	**5µg PIZV**	**10µg PIZV**	**Total**
	(N=30)	**(N=31)**	**(N=31)**	**N=32)**	**(N=124)**
Safety Set (SS)	30 (100%)	31 (100%)	31 (100%)	32(100%)	**124 (100%)**
Full Analysis Set (FAS)	29 (96.7%)	28 (90.3%)	31 (100%)	30 (93.8%)	**118 (95.2%)**
Per-Protocol Set (PPS)	28 (93.3%)	26 (83.9%)	29 (93.5%)	30 (93.8%)	**113 (91.1%)**

Safety Set = all randomized subjects who received at least one (1) dose of PIZV or placebo
Full Analysis Set = all randomized subjects who received at least one dose of PIZV/placebo and provided valid baseline and at least one post-vaccination serology result
Per Protocol Set = all subjects in the FAS who had no major protocol violations

[00391] Subjects in the SS were 35.3 ± 8.91 years of age (mean ± standard deviation), and were distributed as 28.2% in the 18-29 years age-range and 71.8% in the 30-49 years age-range. Women represented 54.8% of the cohort. Study participants were White (81.5%), Black (14.5%), and "Non-Hispanic" (93.5%) regarding race and ethnicity. The mean BMI in the SS was 27.5 ± 4.05 (mean ± standard deviation). Demographic characteristics (age, sex, height, weight, BMI and ethnicity) were overall similar across the four study groups. Women were more represented in the placebo group, where they constituted 66% of the study participants, than in the other groups, where gender distribution was more balanced. The demographics and baseline characteristics are presented in Table 15.

[00392] Safety laboratory parameters and vital signs were checked at study entry as part of inclusion criteria. These specified that vital signs had to be within normal limits (i.e., below Grade 1 as indicated in the FDA Toxicity Grading Scale) and that safety laboratory tests had to be within normal limits or not be above Grade 1 as defined in the FDA Toxicity Grading Scale.

Table 15: Demographic and Baseline Characteristics (Safety Set)

	Number of Subjects (%)				
	Placebo (N=30)	2 ug (N=31)	5 ug (N=31)	10 ug (N=32)	Total (N=124)
Age (Years)					
n	30	31	31	32	124
Mean (SD)	36.5 (9.00)	34.9 (9.52)	35.8 (8.86)	34.1 (8.50)	35.3 (8.91)
Median	39.5	36.0	36.0	33.5	36.0
Minimum, Maximum	18, 49	18, 48	20, 49	20, 49	18, 49
Age (years) (n [%])					
18- 29	8 (26.7)	9 (29.0)	9 (29.0)	9 (28.1)	35 (28.2)
30- 49	22 (73.3)	22 (71.0)	22 (71.0)	23 (71.9)	89 (71.8)
Sex (n [%])					
Male	10 (33.3)	15 (48.4)	13 (41.9)	18 (56.3)	56 (45.2)
Female	20 (66.7)	16 (51.6)	18 (58.1)	14 (43.8)	68 (54.8)
Ethnicity (n [%])					
Hispanic or Latino	1 (3.3)	1 (3.2)	2 (6.5)	4 (12.5)	8 (6.5)
Not-Hispanic or Latino	29 (96.7)	30 (96.8)	29 (93.5)	28 (87.5)	116 (93.5)
Not Reported	0	0	0	0	0
Unknown	0	0	0	0	0
Race (n [%])					
American Indian or Alaskan Native	2 (6.7)	0	0	0	2 (1.6)
Asian	0	0	0	0	0
Black or African American	6 (20.0)	5 (16.1)	3 (9.7)	4 (12.5)	18 (14.5)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	22 (73.3)	26 (83.9)	26 (83.9)	27 (84.4)	101 (81.5)
Multiracial	0	0	2 (6.5)	1 (3.1)	3 (2.4)
BMI (kg/m^2)					
n	30	31	31	32	124
Mean (SD)	28.169 (4.0388)	27.527 (4.7632)	27.541 (3.7165)	26.750 (3.6511)	27.485 (4.0452)
Median	28.861	27.900	27.831	25.965	27.607
Minimum, Maximum	20.86, 34.64	20.13, 34.83	18.84, 34.14	18.80, 34.37	18.80, 34.83

BMI=Weight (kg)/height^2 (m^2).

Note 1: Age is calculated using the Date of Informed Consent.
Note 2: Subject included in Multiracial Category only if multiple Race categories selected.

Safety/ reactogenicity

[00393] The overall reporting incidence of solicited local adverse events (AEs) was higher in the groups that received the vaccine (PIZV) than in the placebo group. Pain was the most frequently reported solicited AE at the injection site. After dose 1, pain was experienced by 30.0% to 38.7% of subjects in the PIZV groups compared to 13.8% in the placebo group. After dose 2, incidences of pain were similar to those following dose 1: 29.6% to 40% in the PIZV groups, and 14.3% in the placebo group. Intensity of pain was reported as mild after dose 1 and mild to moderate after dose 2, with 2 subjects in the 5µg PIZV group (6.7%) and one subject in the 10µg PIZV group (3.3%) reporting moderate pain. Other solicited local AEs (erythema, swelling and induration) were reported by not more than 9.7% of the subjects.

[00394] The onset of pain occurred on day 1 for 90% of the subjects or day 2 (for 3 subjects). Pain was not reported beyond day 5 by any subject in the placebo or PIZV groups.

[00395] Solicited systemic AEs of any nature were reported by 30% to 48.4% of the subjects across the PIZV groups and by 41.4% in the Placebo group after dose 1. After dose 2, incidences were 10% to 33.3% across the PIZV groups and 27.6% in the Placebo group. Overall 81.3% (dose 1) and 75% (dose 2) of the solicited systemic AEs were judged as related to study vaccination. After both doses, the most reported systemic events were headache, fatigue and myalgia.

[00396] Most systemic AEs were reported as mild, i.e. not interfering with daily activity. A few occurrences were moderate in intensity:

[00397] after dose 1, for 6.7-12.9% of subjects in the PIZV groups and 17.2% of placebo recipients;

[00398] after dose 2, for 0 - 3.3% of subjects across the PIZV groups and 10.3% in the placebo group.

[00399] There was a single report of a severe AE: one subject in the placebo group experienced fever. This study participant presented a temperature of 39.4°C, measured orally, 4 days after receiving the second study vaccination. This fever was not judged as study-related by the investigator.

[00400] Solicited systemic AEs were variably reported throughout the 7-day period in the four groups. The onset of events for fever, fatigue, arthralgia and myalgia was mainly during the 2 days following vaccination and was variable for headache and malaise. Fever was reported during the 2 days following vaccination, except for the subject reporting severe fever in the placebo group on day 4.

[00401] The incidence of solicited local and systemic adverse events 7 days after vaccination are shown in Table 16.

Table 16: Incidence of solicited local and systemic adverse events 7 days after vaccination (Safety set)

	Dose 1				Dose 2			
	Placebo (N=30)	**2µg PIZV (N=31)**	**5µg PIZV (N=31)**	**10µg PIZV (N=32)**	**Placebo (N=30)**	**2µg PIZV (N=31)**	**5µg PIZV (N=31)**	**10µg PIZV (N=32)**
Local AEs n (%)								
Any	4 (13.8)	9 (30.0)	12 (38.7)	13 (41.9)	5 (17.9)	8 (29.6)	11 (36.7)	12 (40.0)
Pain	4 (13.8)	9 (30.0)	10 (32.3)	12 (38.7)	4 (14.3)	8 (29.6)	11 (36.7)	12 (40.0)
Erythema	0	0	0	1 (3.2)	1 (3.6)	0	1 (3.3)	1 (3.3)
Swelling	0	0	0	0	0	0	2 (6.7)	0
Induration	0	0	3 (9.7)	2 (6.5)	0	0	1 (3.3)	0
Systemic AEs n (%)								
Any	12 (41.4)	9 (30.0)	12 (38.7)	15 (48.4)	8 (27.6)	9 (33.3)	3 (10.0)	8 (26.7)
Fever	1 (3.4)	0	0	1 (3.2)	2 (7.1)	0	0	0
Headache	9 (31.0)	5 (16.7)	8 (25.8)	4 (12.9)	3 (10.3)	4 (14.8)	1 (3.3)	6 (20.0)
Fatigue	6 (20.7)	7 (23.3)	6 (19.4)	10 (32.3)	6 (20.7)	3 (11.1)	2 (6.7)	5 (16.7)
Arthralgia	1 (3.4)	1 (3.3)	1 (3.2)	3 (9.7)	1 (3.4)	2 (7.4)	0	1 (3.3)
Myalgia	3 (10.3)	3 (10.0)	5 (16.1)	4 (12.9)	2 (6.9)	2 (7.4)	1 (3.3)	2 (6.7)
Malaise	4 (13.8)	2 (6.7)	2 (6.5)	4 (12.9)	2 (6.9)	0	0	3 (10.0)

N= number of subjects with information available; n (%) =number (percentage) of subjects reporting a specific AE.

[00402] In total 30.6% of the subjects reported unsolicited AEs (not including prolonged solicited AEs) in the 28 days following any dose: 21.9-38.7% in the PIZV groups and 36.7% in the placebo group. These AEs were mainly infections, infestations (13.7%) and nervous system disorders (3.2%: headache, migraine, dizziness). All were mild to moderate in intensity.

[00403] Unsolicited AEs were considered as related to the study vaccination for three subjects (2.4%). The events reported were:

[00404] at post dose 1, dizziness for one subject in the 5μg PIZV group and flushing for one subject in the 2μg PIZV group;

[00405] at post dose 2, eye pruritus and lacrimation increased for one subject in the 10μg PIZV group.

[00406] These were mild to moderate in intensity, started on day 1 or 2 after vaccination, had a duration of 1 to 3 days and were all resolved.

[00407] One subject discontinued with the study vaccination due to a headache after dose 1. This subject received PIZV and experienced the headache 1 day after vaccination. The headache was resolved 36 days after its onset. No serious adverse event (SAE) was reported during the period from dose 1 up to 28 days post dose 2.

[00408] The few changes from the baseline observed for blood safety laboratory parameters in the 7 days following vaccination, e.g. from normal to mild or from mild to moderate AEs, occurred in comparable percentages of subjects across the four groups. Urinalysis parameters were either normal at all time-points or the grading category was similar across groups and visits.

Immunogenicity

[00409] Table 17 presents the geometric antibody titers of Zika virus neutralizing antibodies (EC50) as measured by PRNT as well as seropositivity rates and seroconversion rates after each vaccine dose.

[00410] The PIZV vaccine was immunogenic in flavivirus-naïve adults. All subjects were seronegative at baseline. Vaccination of subjects initially seronegative for antibodies against Zika virus elicited seropositivity in all subjects after two doses of PIZV vaccine of any dosage: seroconversion rates ranged from 69.23% to 96.43% post-dose 1 and were 100% post-dose 2. All subjects in the placebo group remained seronegative throughout the period considered.

[00411] A dose-ranging effect was observed on seropositivity rates post-dose 1 and on GMTs after each dose. After the first dose, almost all subjects (96.4%) who had received the 10 μg PIZV dose had mounted neutralizing antibodies against the Zika virus. The

second dose led to a more than10-fold increase in GMT from dose 1, in the three PIZV groups.

Table 17: Seropositivity, seroconversion rates and GMTs of Zika virus neutralizing antibodies (EC_{50}) (PRNT) before and 28 days after administration of each dose of PIZV (Per Protocol Set)

		Placebo (N=28)	**2µg PIZV (N=26)**	**5µg PIZV (N=29)**	**10µg PIZV (N=30)**
Sero-positivity rate (95%CI)	Pre-dose 1	0	0	0	0
	Post-dose 1	0	69.23 (48.21, 85.67)	82.14 (63.11, 93.94)	96.43 (81.65, 99.91)
	Post-dose 2	0	100 (85.75, 100.00)	100 (87.66, 100.00)	100 (87.66, 100.00)
Sero-conversion rate (95%CI)	Post-dose 1	0	69.23 (48.21, 85.67)	82.14 (63.11, 93.94)	96.43 (81.65, 99.91)
	Post-dose 2	0	100 (85.75, 100.00)	100 (87.66, 100.00)	100 (87.66, 100.00)
GMTs (95% CI)	Pre-dose 1	5.00	5.00	5.00	5.00
	Post-dose 1	5.00	38.06 (17.53, 82.66)	93.76 (44.34, 198.30)	291.41 (161.74, 525.06)
	Post-dose 2	5.00	1100.75 (741.07, 1635.00)	1992.33 (1401.28, 2832.70)	3689.89 (2676.75, 5086.49)

N= number of subjects in the PPS with PRNT data available;

Seropositivity is defined as titer ≥ 10; Seroconversion is defined as: seronegative subjects at baseline (titer <10) have titer ≥10 post-vaccination; Results < 10 are assigned a titer of 5; Titers ≥ 10 (limit of detection) and < 26 (lower limit of quantification) are assigned a value of 13.

[00412] The Geometric mean titers determined using PRNT, according to table 17, are shown graphically in Figure 26. The percentage of subjects achieving seroconversion determine using PRNT according to table 17, are shown graphically in Figure 27.

[00413] The distribution of neutralization titers, after dose 1 and after dose 2, are shown in reverse cumulative distribution curves in Figures 28 and 29 respectively.

[00414] In addition to measuring immune response with the PRNT assay, the samples were also tested with the RVP neutralization assay. Table 18 presents the geometric antibody titers of Zika virus neutralizing antibodies (EC50) as measured by the RVP assay. The RVP assay results show a similar dose-ranging effect of the PRNT data, with gradually higher GMTs with increasing PIZV doses.

Table 18: GMTs of Zika virus neutralizing antibodies (EC_{50}) (RVP) before and 28 days after vaccination (Per Protocol Set)

Group		Placebo (N=27)	2 µg PIZV (N=26)	5 µg PIZV (N=28)	10 µg PIZV (N=30)
GMTs (95%CI)	Pre-dose 1	34 (27, 43)	34 (26, 44)	32 (27, 39)	46 (39, 53)
	Post-dose 1	28 (22, 36)	360 (242, 536)	656 (442, 972)	1310 (875, 1961)
	Post-dose 2	31 (25, 40)	3148 (1988, 4986)	6212 (4126, 9354)	13604 (9560, 19359)

N= number of subjects in the PPS with RVP data available.

Conclusion

[00415] The PIZV vaccine was well tolerated and safe for all antigen doses evaluated in the flavivirus-naïve cohort. Solicited systemic AEs were reported in all groups with no apparent increase with increasing dose strength and intensity was mild to moderate. Local solicited AEs reported were also mild to moderate in intensity across the groups. Unsolicited symptoms were reported with similar frequencies in the four study groups. Overall, the vaccine was immunogenic in flavivirus-naïve subjects and a positive dose-ranging response was observed.

Further items of the invention:

1. A vaccine or immunogenic composition comprising a dose of 1µg to 40µg of one antigen from a Zika virus.

2. The vaccine or immunogenic composition of any one of item 1, wherein the Zika virus comprises at least one non-human cell adaptation mutation.

3. A vaccine or immunogenic composition of item 1, the Zika virus having a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

4. The vaccine or immunogenic composition of item 1 or 2, wherein the antigen is a purified inactivated whole virus.

5. The vaccine or immunogenic composition of item 4, wherein the main peak of the purified antigen in the size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

6. The vaccine or immunogenic composition of item 5, wherein the antigen is an inactivated whole virus obtainable from a method wherein the Zika virus is treated with formalin in an amount that ranges from about 0.001% v/v to about 3.0% v/v from 5 to 15 days at a temperature that ranges from about 15ºC to about 37ºC.

7. The vaccine or immunogenic composition of item 5 or 6, wherein the inactivated whole virus is chemically inactivated.

8. The vaccine or immunogenic composition of item 7, wherein the inactivated whole virus is chemically inactivated with one or more of a detergent, formalin, beta-propiolactone (BPL), binary ethylamine (BEI), acetyl ethyleneimine, methylene blue, and psoralen.

9. The vaccine or immunogenic composition of item 8, wherein the inactivated whole virus is chemically inactivated with formalin in a method wherein the Zika virus is treated with formalin in an amount that ranges from about 0.001% v/v to about 3.0% v/v from 5 to 15 days at a temperature that ranges from about 15ºC to about 37ºC.

10. The vaccine or immunogenic composition of any one of items 1 to 9, wherein the vaccine or immunogenic composition comprises a dose of about 2µg of purified inactivated whole virus.

11. The vaccine or immunogenic composition of any one of items 1 to 9, wherein the vaccine or immunogenic composition comprises a dose of about 5µg of purified inactivated whole virus.

12. The vaccine or immunogenic composition of any one of items 1 to 9, wherein the vaccine or immunogenic composition comprises a dose of about 10µg of purified inactivated whole virus.

13. The vaccine or immunogenic composition of item 1, wherein the at least one non-human cell adaptation mutation is in Zika virus Non-structural protein 1 (NS1).

14. The vaccine or immunogenic composition of item 1, wherein the at least one adaptation mutation occurs at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

15. The vaccine or immunogenic composition of any one of items 1 to 14, wherein the at least one adaptation mutation or mutation is a Trp98Gly mutation.

16. The vaccine or immunogenic composition of any one of items 1-15, wherein the at least one adaptation mutation or mutation enhances genetic stability as compared to a Zika virus lacking the at least one adaptation mutation.

17. The vaccine or immunogenic composition of any one of items 1-16, wherein the at least one adaptation mutation or mutation enhances viral replication as compared to a Zika virus lacking the at least one adaptation mutation.

18. The vaccine or immunogenic composition of any one of items 1-17, wherein the Zika virus does not comprise a mutation in Envelope protein E (Env).

19. The vaccine or immunogenic composition of item 1, wherein the non-human cell is a mammalian cell.

20. The vaccine or immunogenic composition of item 1, wherein the non-human cell is a monkey cell.

21. The vaccine or immunogenic composition of item 20, wherein the monkey cell is from a Vero cell line.

22. The vaccine or immunogenic composition of item 21, wherein the Vero cell line is a WHO Vero 10-87 cell line.

23. The vaccine or immunogenic composition of any one of items 1-22, wherein the Zika virus is an African lineage virus or an Asian lineage virus.

24. The vaccine or immunogenic composition of any one of items 1-22, wherein the Zika virus is an Asian lineage virus.

25. The vaccine or immunogenic composition of items 1 to 24, wherein the Zika virus is from strain PRVABC59.

26. The vaccine or immunogenic composition of any one of items 1-25, further comprising an adjuvant.

27. The vaccine or immunogenic composition of item 26, wherein the adjuvant is selected from the group consisting of aluminum salts, toll-like receptor (TLR) agonists, monophosphoryl lipid A (MLA), synthetic lipid A, lipid A mimetics or analogs, MLA derivatives, cytokines, saponins, muramyl dipeptide (MDP) derivatives, CpG oligos, lipopolysaccharide (LPS) of gram-negative bacteria, polyphosphazenes, emulsions, virosomes, cochleates, poly(lactide-co-glycolides) (PLG) microparticles, poloxamer particles, microparticles, liposomes, Complete Freund's Adjuvant (CFA), and Incomplete Freund's Adjuvant (IFA).

28. The vaccine or immunogenic composition of item 27, wherein the adjuvant is an aluminum salt.

29. The vaccine or immunogenic composition of item 28, wherein the adjuvant is selected from the group consisting of alum, aluminum phosphate, aluminum hydroxide, potassium aluminum sulfate, and Alhydrogel 85.

30. The vaccine or immunogenic composition of item 29, wherein the adjuvant is aluminum hydroxide.

31. The vaccine or immunogenic composition of item 30, wherein the vaccine or immunogenic composition comprises 100 µg to 600µg aluminum hydroxide, or 100 µg to

300µg aluminum hydroxide, or 150µg to 250µg aluminum hydroxide, or about 200 µg aluminum hydroxide.

32. The vaccine of any one of items 1 to 31, wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.

33. The vaccine or immunogenic composition of any one of items 1 to 32 further comprising a phosphate buffer and a polyol, such as a sugar, such as sucrose.

34. The vaccine or immunogenic composition of any one of items 1 to 33 comprising

- a dose of about 10µg of purified inactivated whole virus
- about 200 µg aluminum hydroxide,
- a buffer; and optionally
- a sugar such as sucrose.

35. The vaccine or immunogenic composition of any one of items 1 to 34, in the form of a dry substance or aqueous composition.

36. The vaccine or immunogenic composition of any one of items 1 to 34, in the form of an aqueous composition with a volume of from 0.1 to 0.8 ml, or about 0.5ml.

37. A method of treating or preventing, in particular preventing Zika virus infection in a subject in need thereof, comprising administering to the subject the vaccine or immunogenic composition of any one of items 1 to 36.

38. A method for inducing an immune response against a Zika antigen in a subject in need thereof, comprising administering to the subject the vaccine or immunogenic composition of any one of items 1 to 36.

39. A method of preventing Zika virus disease in a fetus or newborn in need thereof, comprising administering to a pregnant subject or a subject that intends to become pregnant or woman of childbearing potential the vaccine of any one of items 1 to 36.

40. The method of preventing Zika virus disease in a subject in need thereof, comprising administering to the subject the vaccine of any one of items 1 to 36.

41. The method of any one of items 37 to 40, wherein the subject is pregnant or intends to become pregnant or is a woman of childbearing potential.

42. The method of any one of items 37 to 41, wherein administration of the vaccine or immunogenic composition induces a protective immune response in the subject.

43. The method of item 42, wherein the protective immune response induced in the subject is greater than a protective immune response induced in a corresponding subject administered a vaccine or immunogenic composition comprising one or more antigens from a Zika virus lacking the at least one non-human cell adaptation mutation.

44. The method of any one of items 37 to 43, wherein administration of the vaccine or immunogenic composition induces the generation of neutralizing antibodies to Zika virus in the subject.

45. The method of any one of items 37 to 44, wherein the administration of the vaccine or immunogenic composition induces the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 10, or greater than 50, or greater than 100, or greater than 200 or greater than 1000, or greater than 1500, or greater than 2000, or greater than 2000, or greater than 3000, as determined by the plaque reduction neutralization test (PRNT)

46. The method of any one of items 37 to 46, wherein the administration of the vaccine or immunogenic composition induces the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 300, or greater than 500, or greater than 1000, or greater than 1500, or greater than 2000, or greater than 3000, or greater than 5000, or greater than 10,000, as determined by the reporter virus particle neutralization assay (RVP).

47. The method of any one of items 45 and 46, wherein such titers are achieved 28 days after the administration.

48. The method of any one of items 37 to 47, wherein severe adverse events are avoided.

49. The method of any one of items 37 to 48, wherein fever of 39°C and higher is avoided.

50. The method of any one of items 37 to 49, wherein the concentration of neutralizing antibodies generated in the subject is higher than a concentration of neutralizing antibodies generated in a corresponding subject administered a vaccine or immunogenic composition comprising one or more antigens from a Zika virus lacking the at least one non-human cell adaptation mutation.

51. The method of any one of items 37 to 50, wherein the vaccine or immunogenic composition is administered by a route selected from the group consisting of subcutaneous administration, transcutaneous administration, intradermal administration, subdermal administration, intramuscular administration, peroral administration, intranasal administration, buccal administration, intraperitoneal administration, intravaginal administration, anal administration and intracranial administration.

52. The method of any one of items 37 to 51, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.

53. The method of any one of items 37 to 52, wherein the vaccine or immunogenic composition is administered one or more times.

54. The method of any one of items 37 to 53, wherein the vaccine or immunogenic composition comprising a dose of 10µg is administered one time.

55. The method of item 54, wherein 14 and/or 28 days after the administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 200 or of greater than 250 is induced, as determined by the plaque reduction neutralization test (PRNT).

56. The method of item 54, wherein 14 and/or 28 days after the administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 1000, or of greater than 2000 is induced, as determined by the reporter virus particle neutralization assay (RVP).

57. The method of any one of items 37 to 53, wherein the vaccine or immunogenic composition comprising a dose of 10 µg is administered as a first (prime) and a second (boost) administration.

58. The method of item 57 wherein the prime and boost administration takes place from about 1 to about 16 weeks apart.

59. The method of item 57 and 58, wherein the second (boost) administration is administered at least 28 days after the first (prime) administration.

60. The method of any one of items 57 to 59, wherein 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 1000, or of greater than 1500, or of greater than 2000, or of greater than 3000 are induced, as determined by the plaque reduction neutralization test (PRNT).

61. The method of any one of items 57 to 59, wherein 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 3000, or of greater than 5000, or of greater than 10000 are induced, as determined by the reporter virus particle neutralization assay (RVP).

62. The method of any one of items 37 to 61, wherein the subject is from a Zika endemic region.

63. The method of any one of items 37 to 62, wherein the subject is from a Zika endemic region subject to an outbreak.

64. The method of any one of items 37 to 61, wherein the subject is from a Zika non-endemic region.

65. The method of any one of items 37 to 61, wherein the subject is from a Zika non-endemic region travelling to an endemic region.

66. The method of any one of items 37 to 65, wherein the subject is flavivirus naive.

67. The method of any one of items 37 to 65, wherein the subject is Hispanic.

68. The method of any one of items 37 to 65, wherein the subject is Latino.

69. The method of any one of items 37 to 65, wherein the subject is American Indian.

70. The method of any one of items 37 to 65, wherein the subject is Alaska native.

71. The method of any one of items 37 to 65, wherein the subject is Asian.

72. The method of any one of items 37 to 65, wherein the subject is Black or African American.

73. The method of any one of items 37 to 65, wherein the subject is Native Hawaiian.

74. The method of any one of items 37 to 65, wherein the subject is White.

75. The method of any one of items 37 to 74, wherein the subject is 18 to 29 years of age, in particular wherein the subject is a woman of childbearing potential.

76. The method of any one of items 37 to 74, wherein the subject is 30 to 49 years of age in particular wherein the subject is a woman of childbearing potential.

77. The vaccine or immunogenic composition of any one of items 1 to 36 for use in a method of any one of items 37 to 76.

78. Use of the vaccine or immunogenic composition of any one of items 1 to 36 in the manufacture of a medicament for the method of any one of items 37 to 76.

79. The vaccine or immunogenic composition of item 32, wherein the plaque purified clonal Zika virus isolate was plaque purified from cells contacted with an inoculum comprising a population of Zika viruses.

80. The vaccine or immunogenic composition of item 79, wherein the cells are non-human cells.

81. The vaccine or immunogenic composition of item 79 or item 80, wherein the cells are insect cells.

82. The vaccine or immunogenic composition of item 81, wherein the insect cells are mosquito cells.

83. The vaccine or immunogenic composition of item 79 or item 80, wherein the cells are mammalian cells.

84. The vaccine or immunogenic composition of item 83, wherein the mammalian cells are monkey cells.

85. The vaccine or immunogenic composition of item 84, wherein the monkey cells are from a Vero cell line.

86. The vaccine or immunogenic composition of item 85, wherein the Vero cell line is a WHO Vero 10-87 cell line.

87. The vaccine or immunogenic composition of any one of items 79 to 85, wherein the population of Zika viruses was heterogeneous.

88. The vaccine or immunogenic composition of any one of items 79 to 86, wherein the population of Zika viruses comprised a Zika virus clinical isolate.

89. The vaccine or immunogenic composition of item 88, wherein the Zika virus clinical isolate is from strain PRVABC59.

90. The vaccine or immunogenic composition of any one of items 79 to 86, wherein the population of Zika viruses comprised a Zika virus that had been previously passaged one or more times in cell culture.

91. The vaccine or immunogenic composition of any one of items 79 to 89, wherein the inoculum comprised human serum.

92. The vaccine or immunogenic composition of any one of items 79 to 90, wherein the inoculum comprised one or more adventitious agents.

93. The vaccine or immunogenic composition of item 91, wherein the plaque purified clonal Zika virus isolate is substantially free of the one or more adventitious agents.

94. The vaccine or immunogenic composition of any one of items 79 to 92, wherein the plaque purified clonal Zika virus isolate is a homogenous genetic population.

95. A method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 300, or greater than 500, or greater than 1000, or greater than 1500, or greater

than 2000, or greater than 3000, as determined by the plaque reduction neutralization test (PRNT).

96. A method for inducing an immune response in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration geometric mean neutralizing antibodies titers in a subject population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 300, or greater than 500, or greater than 1000, or greater than 1500, or greater than 2000, or greater than 3000, or greater than 5000, or greater than 10,000, as determined by the reporter virus particle neutralization assay (RVP).

97. A method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of 100% in a population of at least 20 Zika virus seronegative subjects.

98. A method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a single dose or prime administration, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 10, or greater than 50, or greater than 100, or greater than 200, or greater than 250, as determined by the plaque reduction neutralization test (PRNT).

99. A method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a single dose or prime administration, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 300, or greater than 500, or greater than 1000, or greater than 2000, as determined by the reporter virus particle neutralization assay (RVP).

100. A method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as single dose or prime administration and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 60%, 70%, 80% or 90% in a population of at least 20 Zika virus seronegative subjects.

101. The method of any one of items 95 to 100, wherein the vaccine or immunogenic composition comprises a dose of 1µg to 40µg of the antigen, wherein the antigen is an inactivated whole virus.

102. The method of item 100 or 101, wherein the Zika virus comprises at least one non-human cell adaptation mutation.

103. The method of item 101 or 102, the Zika virus having a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

104. The method of any one of items 101 to 103, wherein the antigen is purified.

105. The method of item 104, wherein the main peak of the purified antigen in the size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

106. The method of items 101 to 105, wherein the antigen is an inactivated whole virus obtainable from a method wherein the Zika virus is treated with formalin in an amount that ranges from about 0.001% v/v to about 3.0% v/v from 5 to 15 days at a temperature that ranges from about 15ºC to about 37ºC.

107. The method of any one of items 100 to 106, wherein the subject is from a Zika endemic region.

108. The method of item 107, wherein the subject is from a Zika endemic region subject to an outbreak.

109. The method of any one of items 100 to 106, wherein the subject is from a Zika non-endemic region.

110. The method of item 109, wherein the subject is from a Zika non-endemic region travelling to an endemic region.

111. The method of any one of items 100 to 110, wherein the subject is flavivirus naive.

112. The method of any one of items 100 to 111, wherein the subject is 18 to 29 years of age, in particular wherein the subject is a woman of childbearing potential.

113. The method of any one of items 100 to 111, wherein the subject is 30 to 49 years of age in particular wherein the subject is a woman of childbearing potential.

114. Vaccine or immunogenic composition comprising one antigen from a Zika virus for use in a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 300, or greater than 500, or greater than 1000, or greater than 1500, or greater than 2000, or greater than 3000, as determined by the plaque reduction neutralization test (PRNT).

115. Vaccine or immunogenic composition comprising one antigen from a Zika virus for use in a method for inducing an immune response in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration geometric mean neutralizing antibodies titers in a subject population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 300, or greater than 500, or greater than 1000, or greater than 1500, or greater than 2000, or greater than 3000, or greater than 5000, or greater than 10,000, as determined by the reporter virus particle neutralization assay (RVP).

116. Vaccine or immunogenic composition comprising one antigen from a Zika virus for use in a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of 100% in a population of at least 20 Zika virus seronegative subjects.

117. Vaccine or immunogenic composition comprising one antigen from a Zika virus for use in a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a single dose or prime administration, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 10, or greater than 50, or greater than 100, or greater than 200, or greater than 250, as determined by the plaque reduction neutralization test (PRNT).

118. Vaccine or immunogenic composition comprising one antigen from a Zika virus for use in a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a single dose or prime administration, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of of greater than 300, or greater than 500, or greater than 1000, or greater than 2000, as determined by the reporter virus particle neutralization assay (RVP).

119. Vaccine or immunogenic composition comprising one antigen from a Zika virus for use in a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as single dose or prime administration and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 60%, 70%, 80% or 90% in a population of at least 20 Zika virus seronegative subjects.

120. Vaccine or immunogenic composition for use of any one of items 114 to 119, wherein the vaccine or immunogenic composition comprises a dose of 1µg to 40µg of the antigen, wherein the antigen is an inactivated whole virus.

121. Vaccine or immunogenic composition for use of item 120, wherein the Zika virus comprises at least one non-human cell adaptation mutation.

122. Vaccine or immunogenic composition for use of item 120 or 121, the Zika virus having a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

123. Vaccine or immunogenic composition for use of items 120 to 122, wherein the antigen is purified.

124. Vaccine or immunogenic composition for use of item 123, wherein the main peak of the purified antigen in the size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

125. Vaccine or immunogenic composition for use of items 120 to 124, wherein the antigen is an inactivated whole virus obtainable from a method wherein the Zika virus is treated with formalin in an amount that ranges from about 0.001% v/v to about 3.0% v/v from 5 to 15 days at a temperature that ranges from about 15ºC to about 37ºC.

126. Vaccine or immunogenic composition for use of any one of items 114 to 125, wherein the subject is from a Zika endemic region.

127. Vaccine or immunogenic composition for use of item 126, wherein the subject is from a Zika endemic region subject to an outbreak.

128. Vaccine or immunogenic composition for use of any one of items 114 to 125, wherein the subject is from a Zika non-endemic region.

129. Vaccine or immunogenic composition for use of item 128, wherein the subject is from a Zika non-endemic region travelling to an endemic region.

130. Vaccine or immunogenic composition for use of any one of items 114 to 129, wherein the subject is flavivirus naïve and/or Zika virus seronegative.

131. Vaccine or immunogenic composition for use of any one of items 114 to 130, wherein the subject is 18 to 29 years of age, in particular wherein the subject is woman of childbearing potential.

132. Vaccine or immunogenic composition for use of any one of items 114 to 130, wherein the subject is 30 to 49 years of age in particular wherein the subject is woman of childbearing potential.

133. A method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart, and wherein the

administration of the vaccine or immunogenic composition induces 28 days after the boost administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects, which are at least 10 times, or at least 15 times, or at least 20 times, or at least 25 times higher than the geometric mean neutralizing antibodies titers induces 28 days after the prime administration, as determined by the plaque reduction neutralization test (PRNT).

134. The method of items 133, wherein the vaccine or immunogenic composition comprises a dose of 1µg to 40µg of the antigen, wherein the antigen is an inactivated whole virus.

135. The method of item 133 or 134, wherein the Zika virus comprises at least one non-human cell adaptation mutation.

136. The method of item 133 or 134, the Zika virus having a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

137. The method of any one of items 133 to 136, wherein the antigen is purified.

138. The method of item 137, wherein the main peak of the purified antigen in the size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

139. The method of items 133 to 138, wherein the antigen is an inactivated whole virus obtainable from a method wherein the Zika virus is treated with formalin in an amount that ranges from about 0.001% v/v to about 3.0% v/v from 5 to 15 days at a temperature that ranges from about 15°C to about 37°C.

140. The method of any one of items 134 to 139, wherein the subject is from a Zika endemic region.

141. The method of item 140, wherein the subject is from a Zika endemic region subject to an outbreak.

142. The method of any one of items 133 to 139, wherein the subject is from a Zika non-endemic region.

143. The method of item 142, wherein the subject is from a Zika non-endemic region travelling to an endemic region.

144. The method of any one of items 133 to 143, wherein the subject is flavivirus naive.

145. The method of any one of items 133 to 144, wherein the subject is 18 to 29 years of age, in particular wherein the subject is a woman of childbearing potential.

146. The method of any one of items 133 to 144, wherein the subject is 30 to 49 years of age in particular wherein the subject is a woman of childbearing potential.

147. Vaccine or immunogenic composition comprising one antigen from a Zika virus for use in a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart, and wherein the administration of the vaccine or immunogenic composition induces 28 days after the boost administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects, which are at least 10 times, or at least 15 times, or at least 20 times, or at least 25 times higher than the geometric mean neutralizing antibodies titers induces 28 days after the prime administration, as determined by the plaque reduction neutralization test (PRNT).

148. Vaccine or immunogenic composition for use of item 147, wherein the vaccine or immunogenic composition comprises a dose of 1µg to 40µg of the antigen, wherein the antigen is an inactivated whole virus.

149. Vaccine or immunogenic composition for use of item 147 or 148, wherein the Zika virus comprises at least one non-human cell adaptation mutation.

150. Vaccine or immunogenic composition for use of item 147 or 148, the Zika virus having a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

151. Vaccine or immunogenic composition for use of items 147 to 150, wherein the antigen is purified.

152. Vaccine or immunogenic composition for use of item 151, wherein the main peak of the purified antigen in the size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

153. Vaccine or immunogenic composition for use of items 148 to 152, wherein the antigen is an inactivated whole virus obtainable from a method wherein the Zika virus is treated with formalin in an amount that ranges from about 0.001% v/v to about 3.0% v/v from 5 to 15 days at a temperature that ranges from about 15ºC to about 37ºC.

154. Vaccine or immunogenic composition for use of any one of items 147 to 153, wherein the subject is from a Zika endemic region.

155. Vaccine or immunogenic composition for use of item 154, wherein the subject is from a Zika endemic region subject to an outbreak.

156. Vaccine or immunogenic composition for use of any one of items 147 to 153, wherein the subject is from a Zika non-endemic region.

157. Vaccine or immunogenic composition for use of item 156, wherein the subject is from a Zika non-endemic region travelling to an endemic region.

158. Vaccine or immunogenic composition for use of any one of items 147 to 157, wherein the subject is flavivirus naïve and/or Zika virus seronegative.

159. Vaccine or immunogenic composition for use of any one of items 147 to 157, wherein the subject is 18 to 29 years of age, in particular wherein the subject is woman of childbearing potential.

160. Vaccine or immunogenic composition for use of any one of items 147 to 157, wherein the subject is 30 to 49 years of age in particular wherein the subject is woman of childbearing potential.

CLAIMS

What is claimed is:

1. A vaccine or immunogenic composition comprising a dose of 1µg to 40µg of one antigen from a Zika virus, wherein the antigen is an inactivated whole virus.

2. A vaccine or immunogenic composition of claim 1, the Zika virus having a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

3. The vaccine or immunogenic composition of claim 1 or 2, wherein the antigen is purified.

4. The vaccine or immunogenic composition of claim 3, wherein the main peak of the purified antigen in the size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

5. The vaccine or immunogenic composition of any one of claims 1 to 5, wherein the vaccine or immunogenic composition comprises a dose of about 2µg of purified inactivated whole virus.

6. The vaccine or immunogenic composition of any one of claims 1 to 5, wherein the vaccine or immunogenic composition comprises a dose of about 5µg of purified inactivated whole virus.

7. The vaccine or immunogenic composition of any one of claims 1 to 5, wherein the vaccine or immunogenic composition comprises a dose of about 10µg of purified inactivated whole virus.

8. The vaccine or immunogenic composition of any one of claims 1 to 7, wherein the at least one adaptation mutation or mutation is a Trp98Gly mutation.

9. The vaccine or immunogenic composition of claims 1 to 8, wherein the Zika virus is from strain PRVABC59.

10. The vaccine or immunogenic composition of any one of claims 1-9, further comprising an adjuvant.

11. The vaccine or immunogenic composition of claim 10, wherein the adjuvant is aluminum hydroxide.

12. The vaccine or immunogenic composition of claim 11, wherein the vaccine or immunogenic composition comprises 100 µg to 600µg aluminum hydroxide, or 100 µg to 300µg aluminum hydroxide, or 150µg to 250µg aluminum hydroxide, or about 200 µg aluminum hydroxide.

13. The vaccine of any one of claims 1 to 12, wherein the Zika virus is a clonal isolate, in particular from a plaque purified clonal Zika virus isolate.

14. The vaccine or immunogenic composition of any one of claims 1 to 13 comprising

- a dose of about 10µg of purified inactivated whole virus
- about 200 µg aluminum hydroxide,
- a buffer; and optionally
- a sugar such as sucrose.

15. A method of treating or preventing, in particular preventing Zika virus infection in a subject in need thereof, comprising administering to the subject the vaccine or immunogenic composition of any one of claims 1 to 14.

16. A method for inducing an immune response against a Zika antigen in a subject in need thereof, comprising administering to the subject the vaccine or immunogenic composition of any one of claims 1 to 14.

17. A method of preventing Zika virus disease in a fetus or newborn in need thereof, comprising administering to a pregnant subject or a subject that intends to become pregnant or woman of childbearing potential the vaccine of any one of claims 1 to 14.

18. The method of preventing Zika virus disease in a subject in need thereof, comprising administering to the subject the vaccine of any one of claims 1 to 14.

19. The method of any one of claims 15 to 18, wherein the subject is pregnant or intends to become pregnant or in a woman of childbearing potential.

20. The method of any one of claims 15 to 19, wherein severe adverse events are avoided.

21. The method of any one of claims 15 to 19, wherein fever of 39°C and higher is avoided.

22. The method of any one of claims 15 to 21, wherein the vaccine or immunogenic composition is administered by intramuscular or subcutaneous administration.

23. The method of any one of claims 15 to 22, wherein the vaccine or immunogenic composition is administered one or more times.

24. The method of any one of claims 15 to 23, wherein the vaccine or immunogenic composition comprising a dose of 10µg is administered one time.

25. The method of claims 23 to 24, wherein 14 and/or 28 days after the first administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 200 or of greater than 250 is induced, as determined by the plaque reduction neutralization test (PRNT).

26. The method of any one of claims 15 to 22, wherein the vaccine or immunogenic composition comprising a dose of 10 µg is administered as a first (prime) and a second (boost) administration.

27. The method of claim 26 wherein the prime and boost administration takes place from about 1 to about 16 weeks apart.

28. The method of claim 26 and 27, wherein the second (boost) administration is administered at least 28 days after the first (prime) administration.

29. The method of any one of claims 26 to 28, wherein 14 and/or 28 days after the boost administration of the vaccine or immunogenic composition the generation of neutralizing antibodies titers to Zika virus in a subject of greater than 1000, or of greater than 1500, or of greater than 2000, or of greater than 3000 are induced, as determined by the plaque reduction neutralization test (PRNT).

30. The method of any one of claims 15 to 29, wherein the subject is from a Zika endemic region, optionally subject to an outbreak.

31. The method of any one of claims 15 to 29, wherein the subject is from a Zika non-endemic region travelling to an endemic region.

32. The method of any one of claims 15 to 31, wherein the subject is 18 to 29 years of age, in particular wherein the subject is a female subject.

33. The method of any one of claims 15 to 31, wherein the subject is 30 to 49 years of age in particular wherein the subject is a female subject.

34. The vaccine or immunogenic composition of any one of claims 1 to 14 for use in a method of any one of claims 15 to 33.

35. Use of the vaccine or immunogenic composition of any one of claims 1 to 14 in the manufacture of a medicament for the method of any one of claims 15 to 33.

36. Vaccine or immunogenic composition comprising one antigen from a Zika virus for use in a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 1500, or greater than 2000, or greater than 3000, as determined by the plaque reduction neutralization test (PRNT).

37. Vaccine or immunogenic composition comprising one antigen from a Zika virus for use in a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration a seroconversion rate of 100% in a population of at least 20 Zika virus seronegative subjects.

38. Vaccine or immunogenic composition comprising one antigen from a Zika virus for use in a method of treating or preventing, in particular preventing Zika virus infection in a

subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a single dose or prime administration, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects of greater than 200, or greater than 250, as determined by the plaque reduction neutralization test (PRNT).

39. Vaccine or immunogenic composition comprising one antigen from a Zika virus for use in a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as single dose or prime administration and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the single dose or prime administration a seroconversion rate of 60%, 70%, 80% or 90% in a population of at least 20 Zika virus seronegative subjects.

40. Vaccine or immunogenic composition for use of any one of claims 36 to 39, wherein the vaccine or immunogenic composition comprises a dose of 1µg to 40µg of the antigen, wherein the antigen is an inactivated whole virus.

41. Vaccine or immunogenic composition for use of claim 40, the Zika virus having a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

42. Vaccine or immunogenic composition for use of claims 40 to 41, wherein the antigen is purified, and wherein the main peak of the purified antigen in the size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

43. Vaccine or immunogenic composition for use of any one of claims 36 to 42, wherein the subject is from a Zika endemic region, optionally subject to an outbreak.

44. Vaccine or immunogenic composition for use of any one of claims 36 to 42, wherein the subject is from a Zika non-endemic region travelling to an endemic region.

45. Vaccine or immunogenic composition for use of any one of claims 36 to 44, wherein the subject is 18 to 29 years of age, in particular wherein the subject is woman of childbearing potential.

46. Vaccine or immunogenic composition for use of any one of claims 36 to 44, wherein the subject is 30 to 49 years of age in particular wherein the subject is woman of childbearing potential.

47. Vaccine or immunogenic composition comprising one antigen from a Zika virus for use in a method of treating or preventing, in particular preventing Zika virus infection in a subject population in need thereof, comprising administering to individual subjects of said subject population a vaccine or immunogenic composition comprising one antigen from a Zika virus, wherein the vaccine or immunogenic composition is administered as a first (prime) and a second (boost) administration about 1 to about 16 weeks apart, and wherein the administration of the vaccine or immunogenic composition induces 14 and/or 28 days after the boost administration geometric mean neutralizing antibodies titers in a population of at least 20 flavivirus naïve subjects and/or at least 20 Zika virus seronegative subjects, which are at least 10 times, or at least 15 times, or at least 20 times, or at least 25 times higher than the geometric mean neutralizing antibodies titers induces 28 days after the prime administration, as determined by the plaque reduction neutralization test (PRNT).

48. Vaccine or immunogenic composition for use of claim 47, wherein the vaccine or immunogenic composition comprises a dose of 1µg to 40µg of the antigen, wherein the antigen is an inactivated whole virus.

49. Vaccine or immunogenic composition for use of claim 48, the Zika virus having a mutation at position 98 of SEQ ID NO: 1, or at a position corresponding to position 98 of SEQ ID NO: 1.

50. Vaccine or immunogenic composition for use of claims 47 to 49, wherein the antigen is purified, and wherein the main peak of the purified antigen in the size exclusion chromatography is more than 85% of the total area under the curve in the size exclusion chromatography.

51. Vaccine or immunogenic composition for use of any one of claims 47 to 50, wherein the subject is from a Zika endemic region, optionally subject to an outbreak.

52. Vaccine or immunogenic composition for use of any one of claims 47 to 50, wherein the subject is from a Zika non-endemic region travelling to an endemic region.

53. Vaccine or immunogenic composition for use of any one of claims 47 to 52, wherein the subject is 18 to 29 years of age, in particular wherein the subject is woman of childbearing potential.

54. Vaccine or immunogenic composition for use of any one of claims 47 to 52, wherein the subject is 30 to 49 years of age in particular wherein the subject is woman of childbearing potential.

ABSTRACT

The present disclosure relates to Zika virus vaccines and immunogenic compositions having one or more antigens from a Zika virus (*e.g.,* a Zika virus clonal isolate, a non-human cell adapted Zika virus, *etc.*), and methods of treatments and uses thereof.