

Figure 17

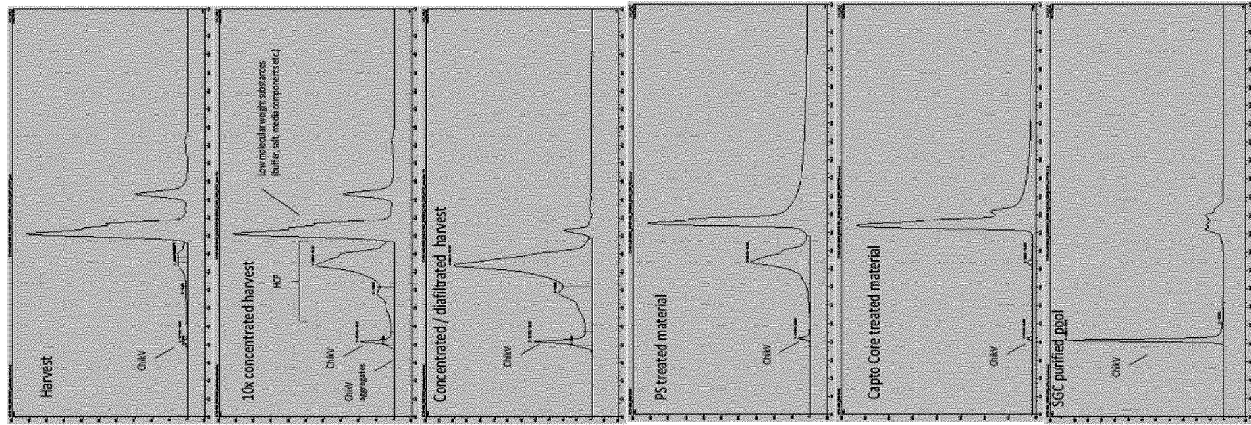


Figure 18a

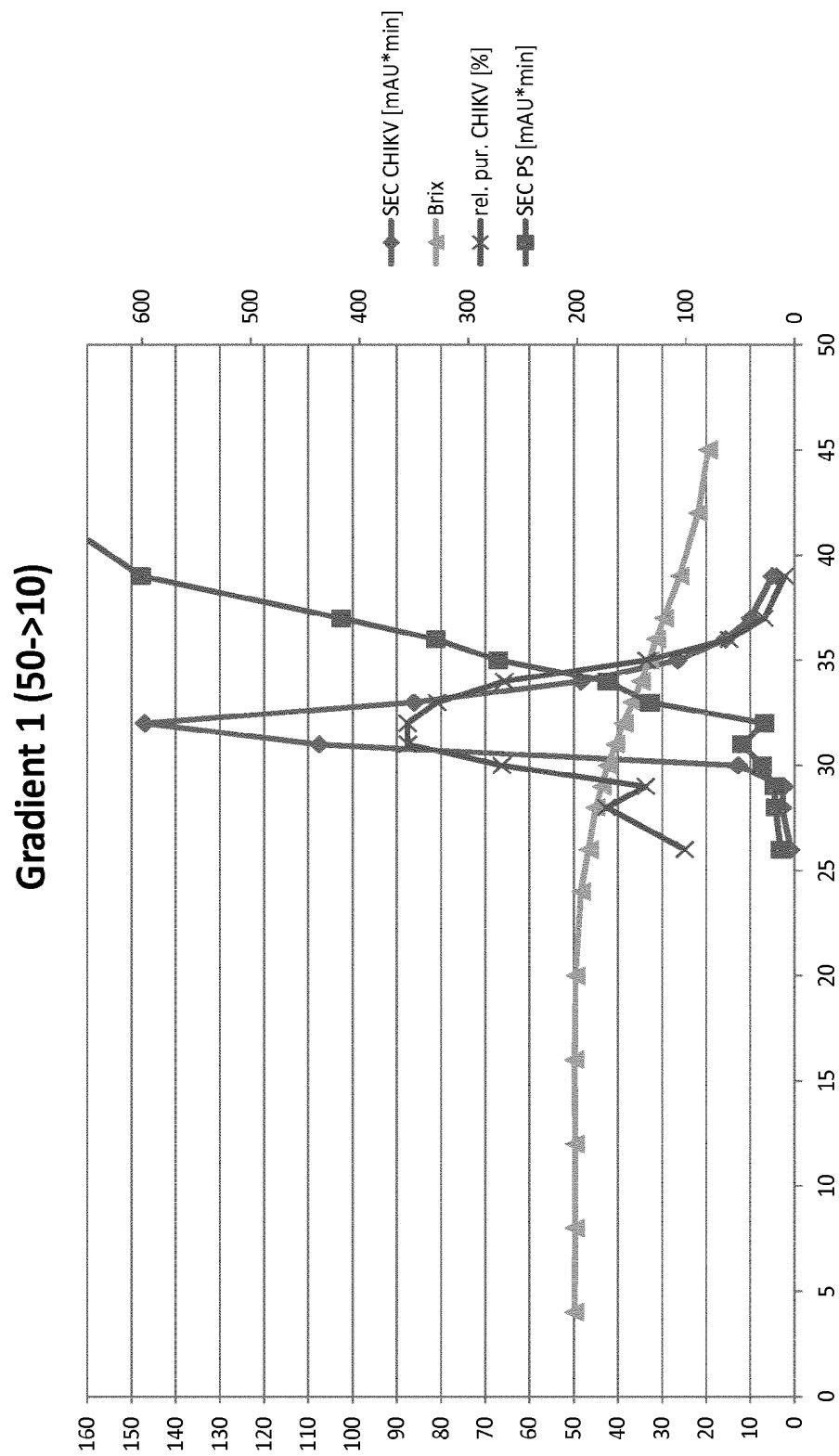


Figure 18b

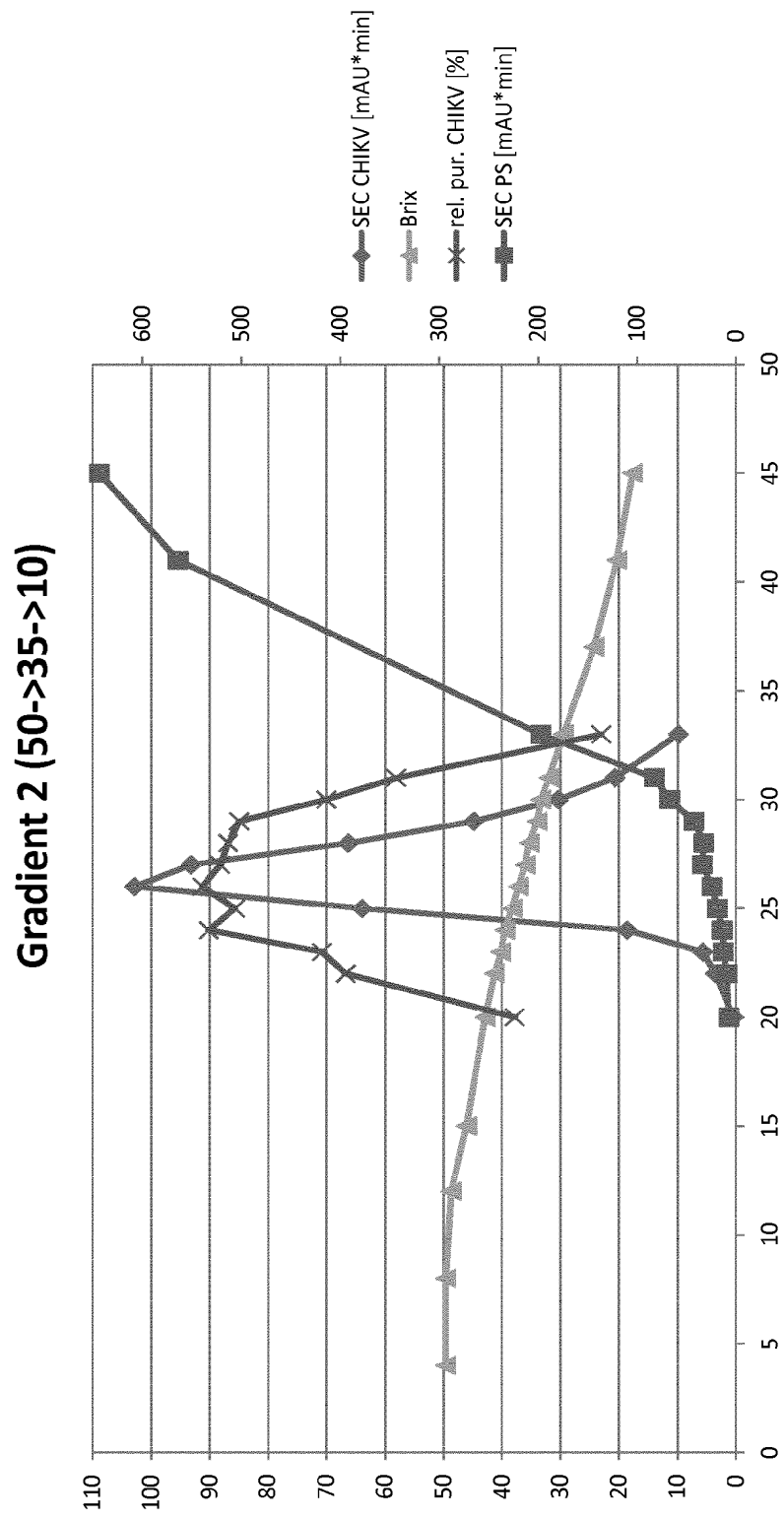


Figure 18c

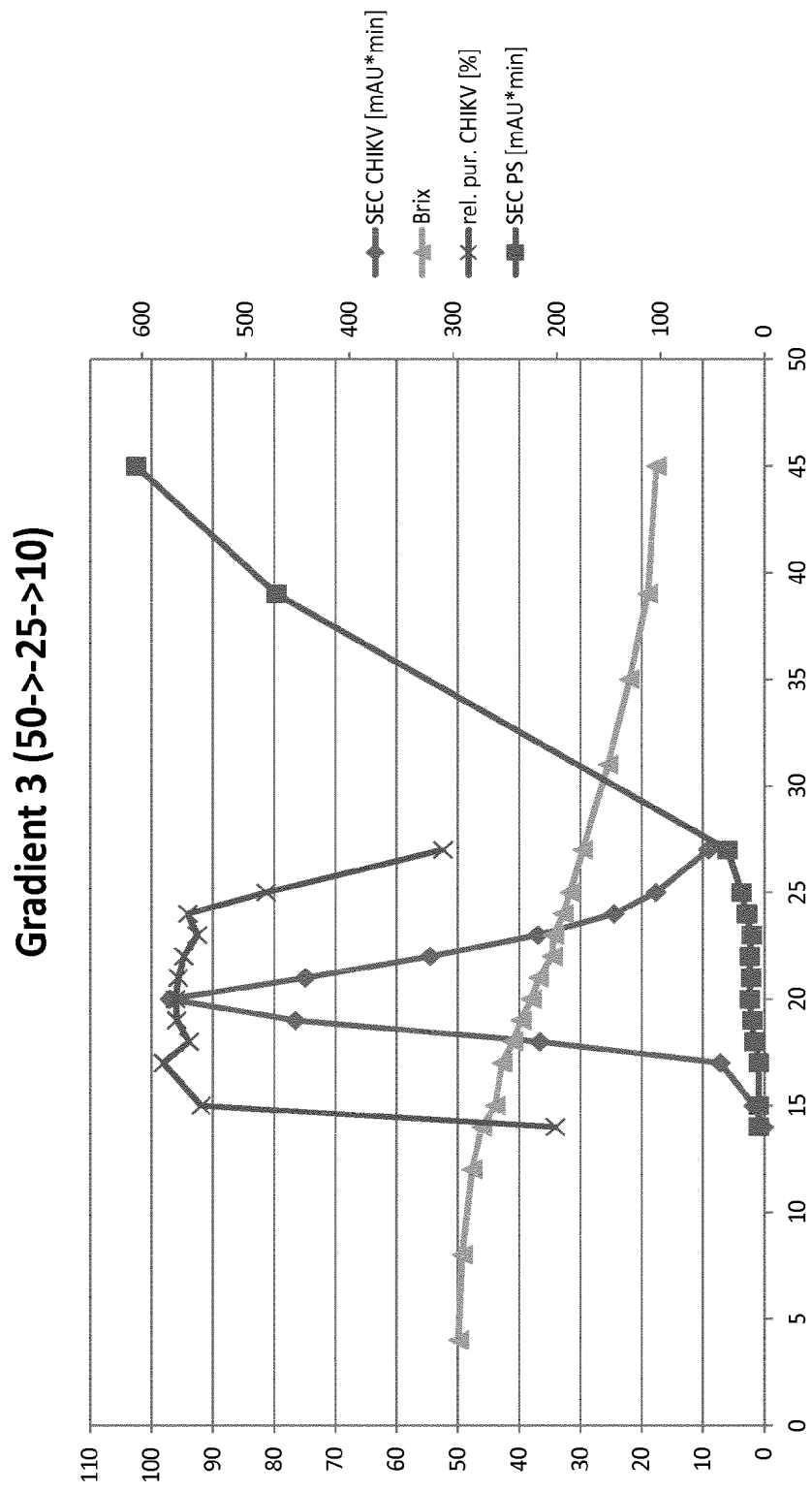


Figure 18d

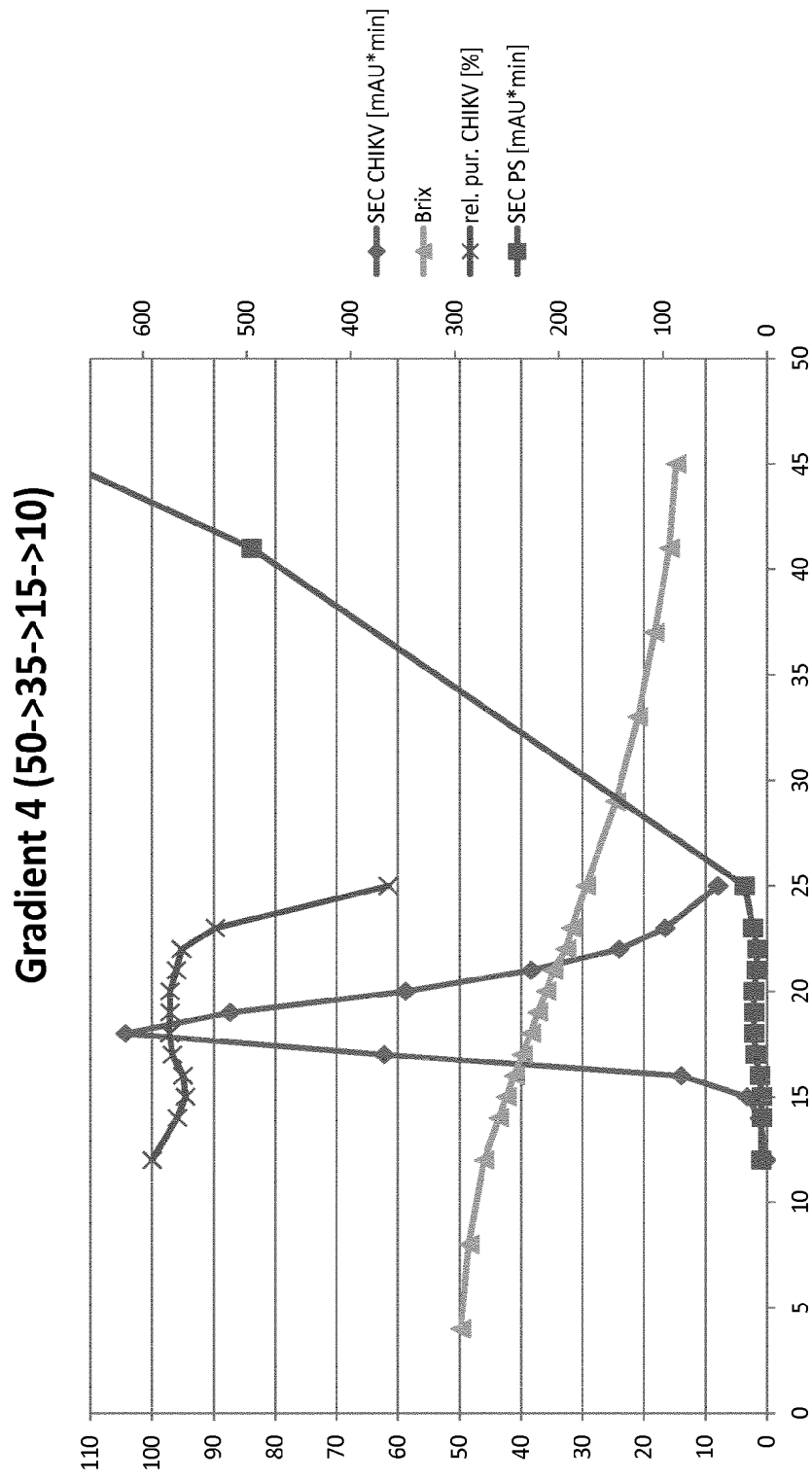


Figure 19

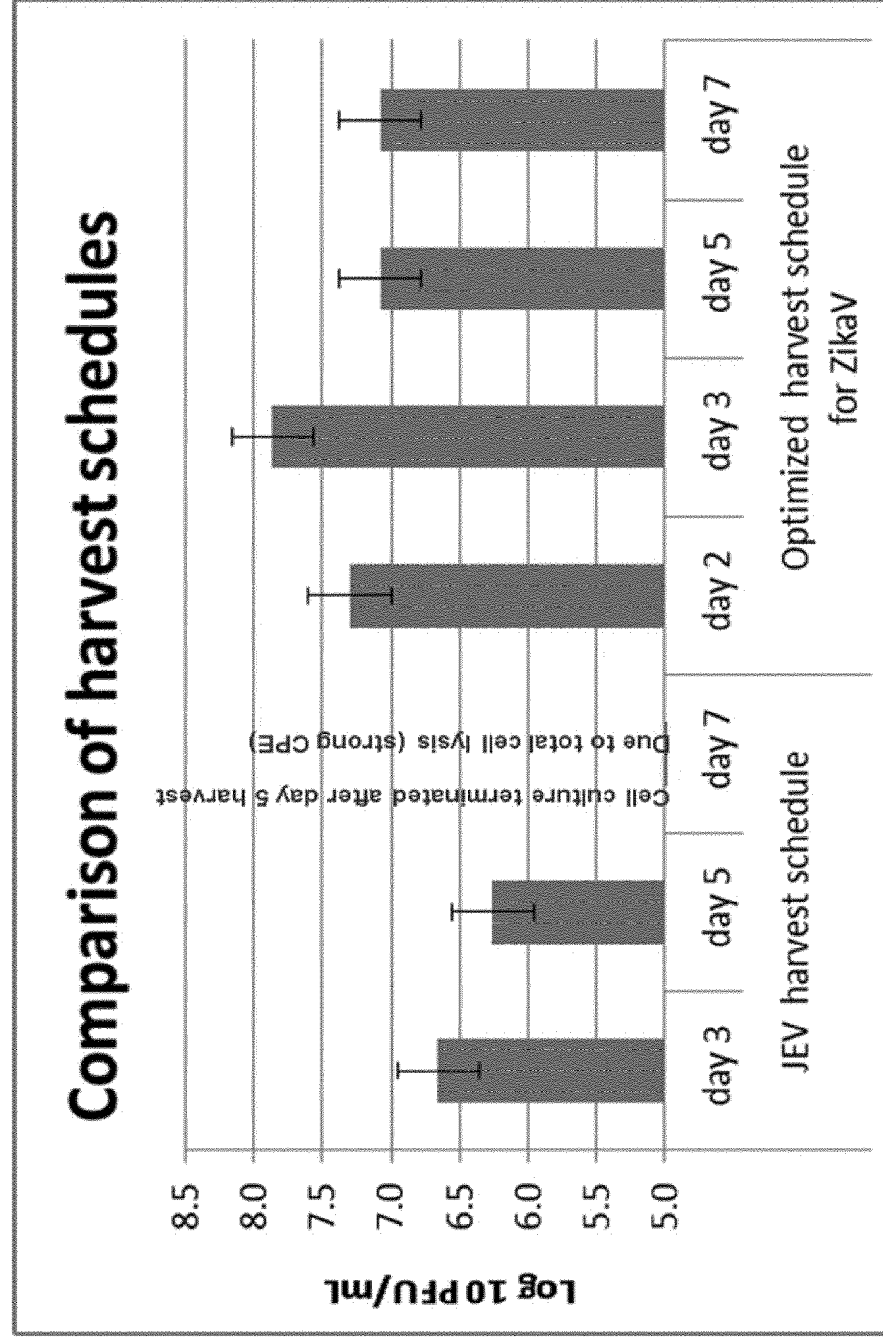


Figure 20

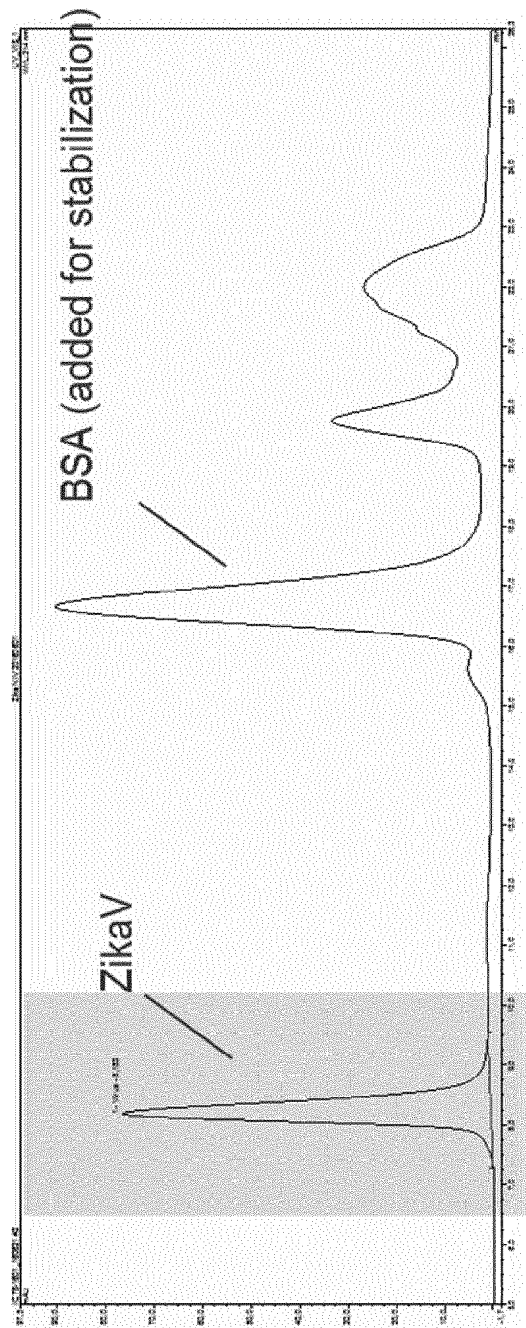
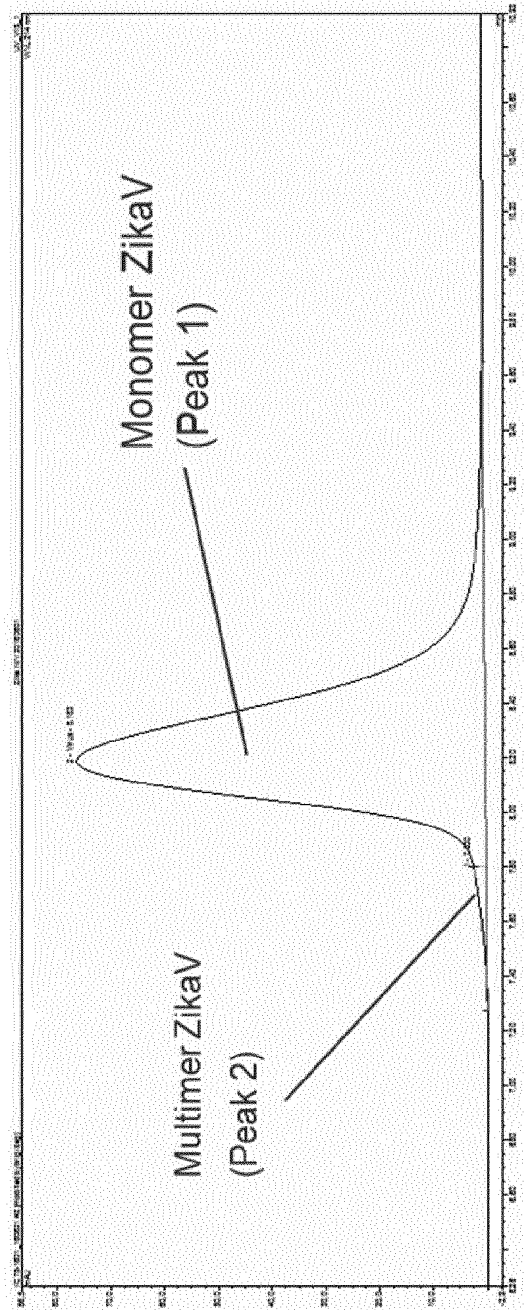


Figure 21

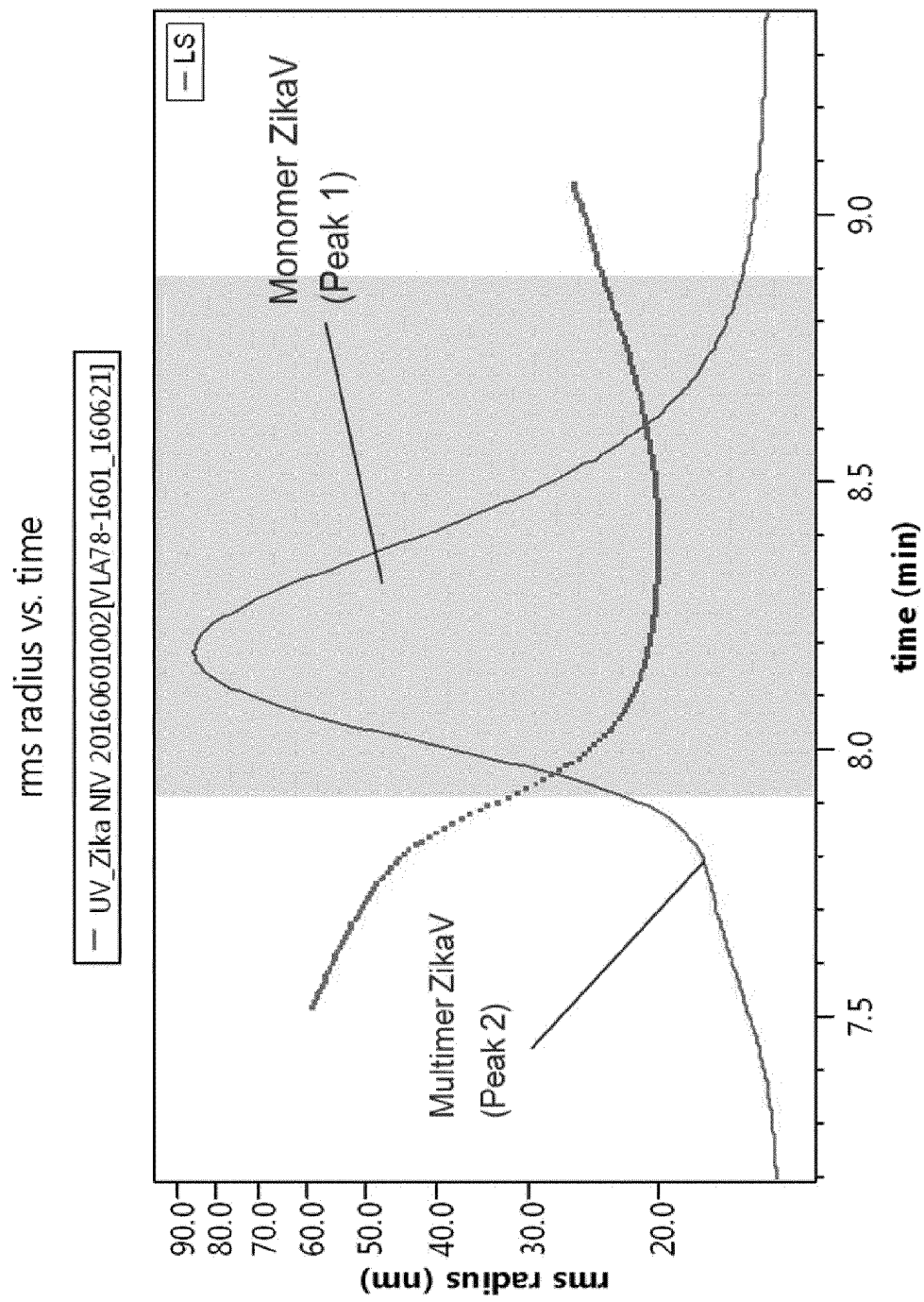


Figure 22

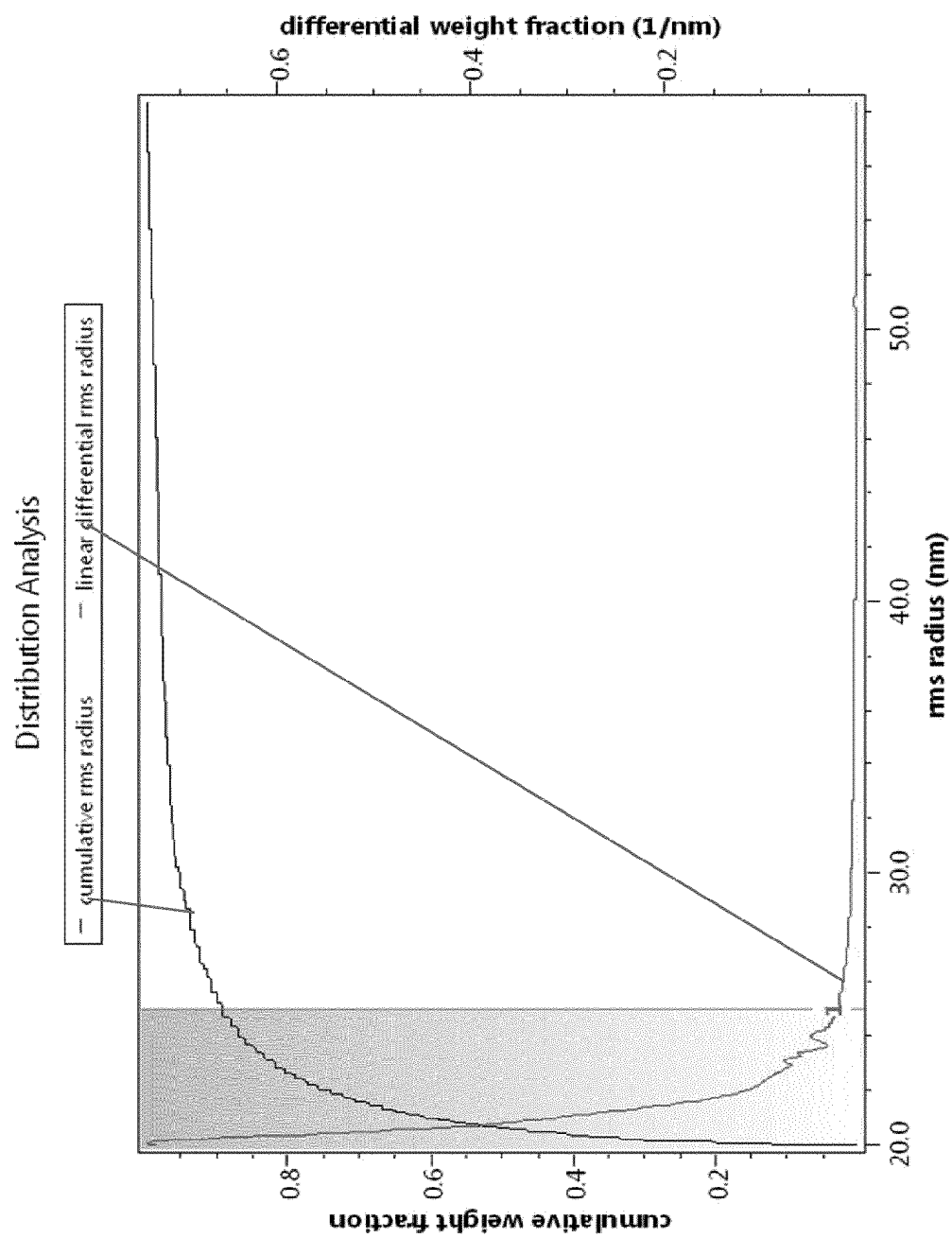


Figure 23

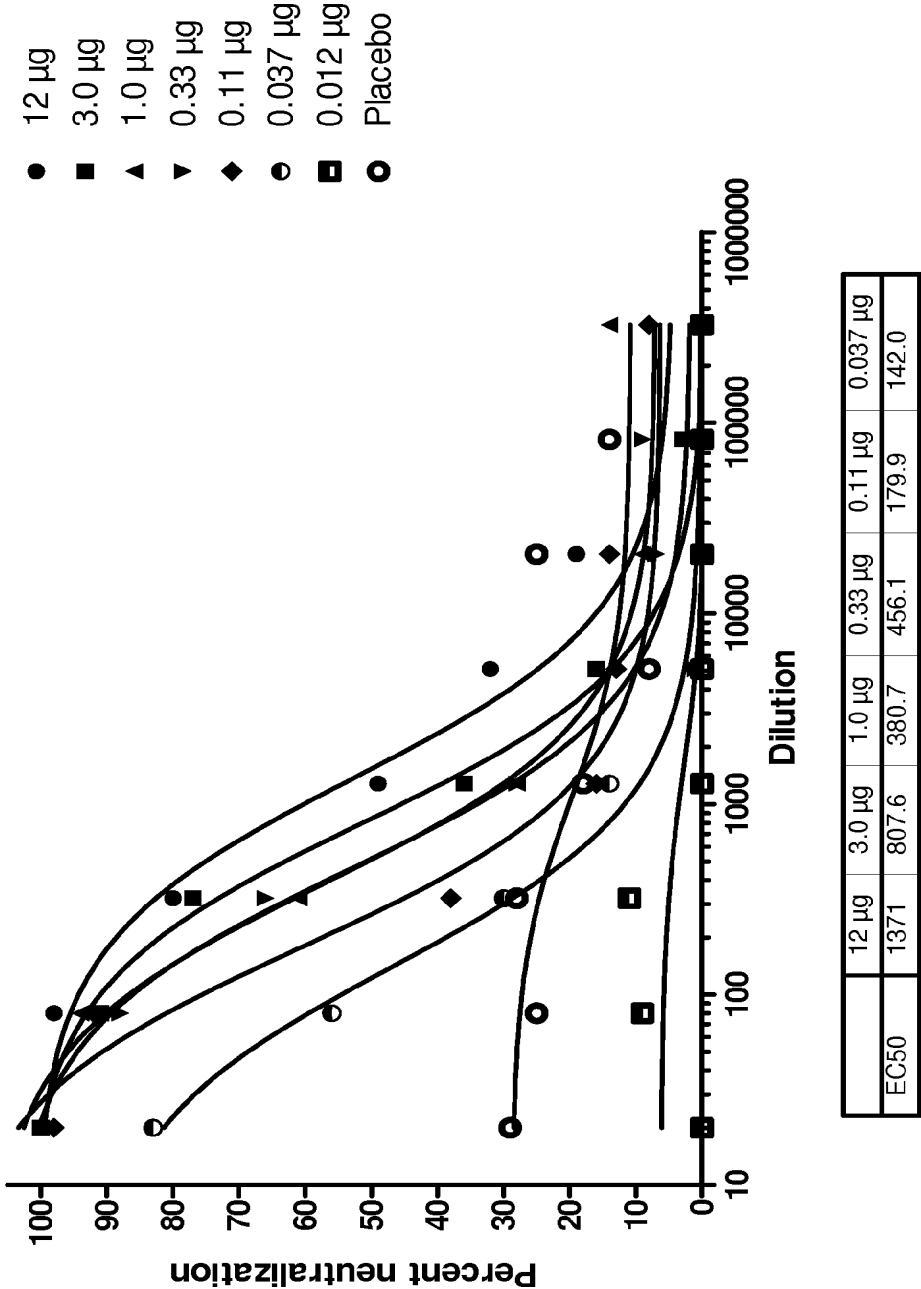
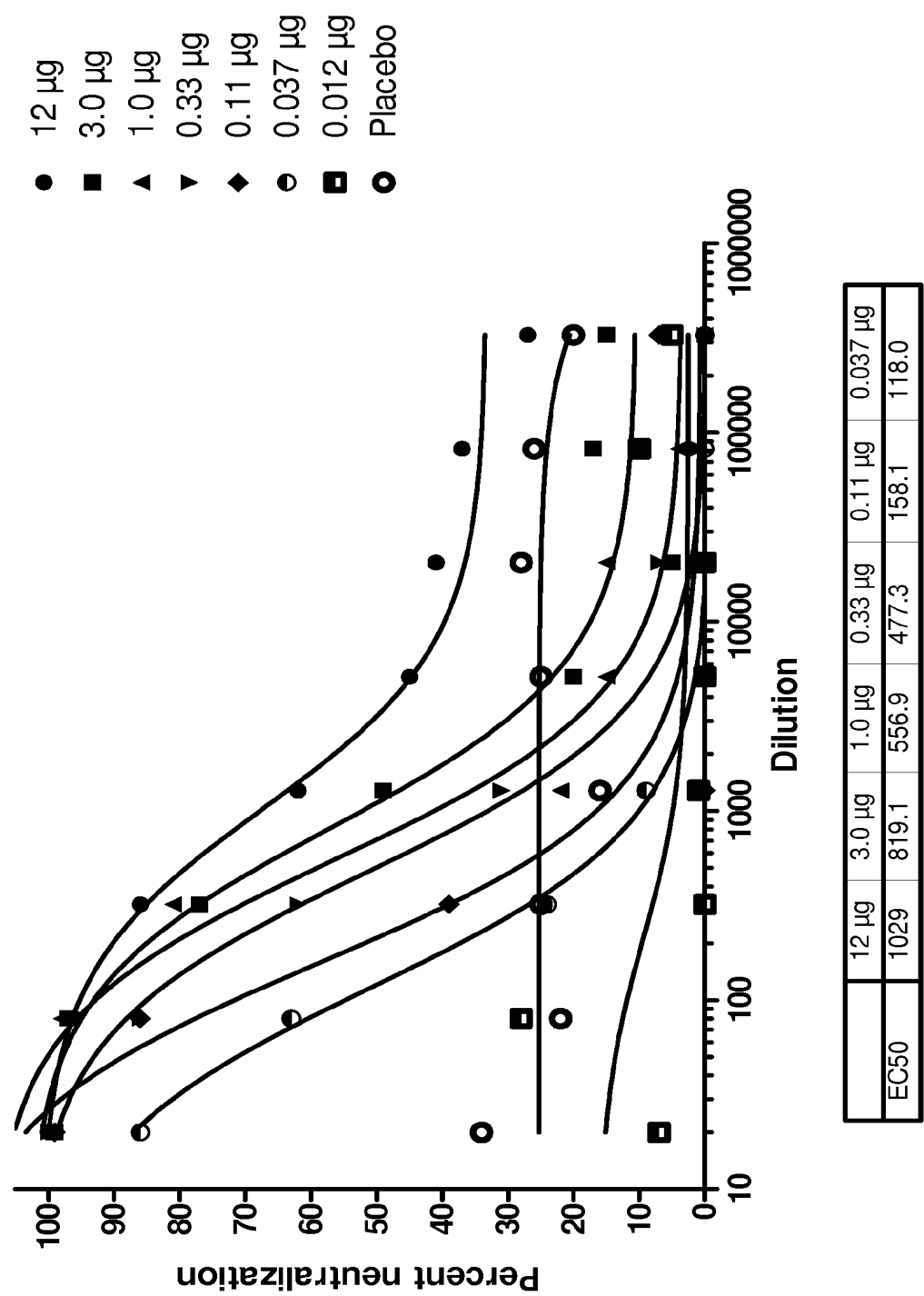


Figure 24



Bescheinigung

Die angehefteten
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geltenden Fassung der auf
dem nächsten Blatt
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Patentanmeldung Nr.

Patent application No.

Demande de brevet n°

16176025.1 / EP16176025

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP16176025.

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.



V. Joseph

Anmeldung Nr:
Application no.: **16176025.1**
Demande no. :

Anmeldetag:
Date of filing: **23.06.16**
Date de dépôt :

Anmelder / Applicant(s) / Demandeur(s):

Valneva SE
World Trade Center Lyon, Tour Oxygène
10-12 Boulevard Marius Vivier Merle
69003 Lyon/FR

Bezeichnung der Erfindung / Title of the invention / Titre de l'invention:

(Falls die Bezeichnung der Erfindung nicht angegeben ist, oder falls die Anmeldung in einer Nicht-Amtssprache des EPA eingereicht wurde, siehe Beschreibung bezüglich ursprünglicher Bezeichnung.

If no title is shown, or if the application has been filed in a non-EPO language, please refer to the description for the original title.

Si aucun titre n'est indiqué, ou si la demande a été déposée dans une langue autre qu'une langue officielle de l'OEB, se référer à la description pour le titre original.)

VIRUS PURIFICATION

In Anspruch genommene Priorität(en) / Priority(Priorities) claimed / Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen / State/Date/File no. / Pays/Date/Numéro de dépôt:

Am Anmeldetag benannte Vertragsstaaten / Contracting States designated at date of filing / Etats contractants désignées lors du dépôt:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL
PT RO RS SE SI SK SM TR

VIRUS PURIFICATION

FIELD OF INVENTION

The disclosure relates to methods for the purification of viruses for use in vaccines and in particular relates to an improved sucrose gradient process step allowing the separation of impurities such as protamine sulphate.

The disclosure also relates to Zika virus vaccines and compositions and methods for producing said vaccines and administering the vaccines to subjects for the generation of an anti-Zika virus immune response.

BACKGROUND OF THE INVENTION

Adverse responses to protamine sulfate have been known for many years. Previous exposure to protamine can induce a humoral immune response and predispose susceptible individuals to the development of untoward reactions from the subsequent use of this drug. Patients exposed to protamine through the use of protamine-containing insulin or during heparin neutralization may experience life-threatening reactions and fatal anaphylaxis upon receiving large doses of protamine intravenously. Severe reactions to intravenous protamine can occur in the absence of local or systemic allergic reactions to subcutaneous injection of protamine-containing insulin. Although there is no clear evidence for hypersensitivity reactions of protamine sulphate linked to vaccination, vaccines containing protamine impurities have a precaution and contraindication warning in their labels stating that a serious allergic reaction after a previous dose of such a protamine containing vaccine (e.g. IXIARO®, see CDC site <http://www.cdc.gov/japaneseencephalitis/vaccine/>) is a contraindication to further doses. Thus elimination of said impurity is a medical request for an improved safety profile. On the other hand protamine sulphate is an excellent tool (and often better than other tools such as benzonase) to purify crude harvests of viruses grown on cell substrates.

In 2007, Zika virus was detected for the first time outside of the endemic regions of Asia and Africa since its discovery in a Rhesus monkey in Uganda in 1947. Since then, the virus has caused a large epidemic in French Polynesia, spreading through islands in the Pacific and into South and Central America by 2015 (WHO “Zika Situation Report” February 5, 2016). Evidence suggests that in addition to being transmitted by *Aedes* species

mosquitos, other vectors may exist, and the virus may be transmitted by blood transfusion, transplacentally, and through sexual transmission (WHO Zika Virus Fact Sheet, Feb. 2016). Though the symptoms of Zika virus infection include mild fever, rash, and conjunctivitis, there is a likely correlation between infection and neurological disorders, including Guillain-

5 Barré syndrome and microcephaly in fetuses/neonates subsequent to infection during pregnancy. There is currently no specific treatment or vaccine for Zika virus and the only preventative measurements involve control of the mosquito vector. Zika virus presents a substantial public health threat due to the wide circulation of the *Aedes* mosquito, multiple routes of transmission, and potentially severe neurological effects of infection.

10

SUMMARY OF THE INVENTION

During the course of virus purification, it was observed that addition of protamine sulfate to a virus harvest produced on a cell substrate removed not only contaminating DNA

15 derived from host cells, as expected, but surprisingly also virtually eliminated immature and otherwise non-infectious virus particles from the preparation. This finding provided a streamlined, gentle, reproducible and broadly-applicable process for obtaining highly-purified infectious virus particles for applications such as vaccine preparation. In addition, it was surprisingly found that said protamine sulfate can very efficiently be separated from the virus

20 fraction allowing for a safer vaccine produced at high yields.

Disclosed herein are virus vaccines and compositions comprising an inactivated virus, and related methods of producing said vaccines and compositions. Also provided are methods of administering said virus vaccines for the prevention of virus infection and/or for the production of an anti-virus immune response in subjects, for example subjects at risk of

25 being exposed to virus. In particular, the invention is directed to a virus vaccine comprising an optimally inactivated virus particle, wherein the virus particle in an appropriate dose is able to seroconvert a subject that is administered the virus vaccine with at least a 70% probability, preferably an 80% probability. Another advantage of the invention is that related methods of producing said vaccines and compositions are very efficient and provide

30 pure compositions largely void of impurities, in particular protamine sulphate, allowing for high volume production of vaccines. Examples to the above are provided for Zika virus and Chikungunya virus.

Each of the limitations of the invention can encompass various embodiments of the invention. It is, therefore, anticipated that each of the limitations of the invention involving any one element or combinations of elements can be included in each aspect of the invention. This invention is not limited in its application to the details of construction and the
 5 arrangement of components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways.

BRIEF DESCRIPTION OF THE DRAWINGS

10 The accompanying drawings are not intended to be drawn to scale. The figures are illustrative only and are not required for enablement of the disclosure. For purposes of clarity, not every component may be labeled in every drawing, alignments were performed with the multi alignment package Jalview (Waterhouse et al., 2009, Bioinformatics 25 (9) 1189-1191). In the drawings:

15 Figure 1: Average distance tree (by % identity, nt), complete genomes.

Figure 2: Neighbor joining tree (by % identity, nt), complete genomes.

Figure 3: Pairwise alignment-Jalview (% identity, nt), complete genomes.

Figure 4: Average distance tree (by % identity, aa), E-protein.

20 Figure 5: Neighbor joining tree (by % identity, aa), E-protein.

Figure 6: Pairwise alignment-Jalview (% identity, aa), E-protein.

Figure 7: Alignment (blue shading: % identity, aa), E-protein.

Figure 8a: Overview of an efficient Zika virus purification process.

Figure 8b: Overview of an efficient inactivation step.

25 Figure 9: SEC-HPLC of individual 30x concentrated Zika harvest prior PS treatment

Figure 10: SEC-HPLC of individual 30x concentrated Zika harvest post PS treatment

Figure 11: Preparation of the sucrose gradient.

Figure 12: Representative SDS-PAGE from the sucrose gradient harvest of a Zika purification is shown.

30 Figure 13: Schematic separation of Virus (ChikV as an example) and PS/HPC using the optimized 3-layer sucrose gradient centrifugation process.

Figure 14: Correlation between JEV Antigen content in NIV analysed by ELISA and SEC-HPLC (Dionex Ultimate 3000, Superose 6 column).

Figure 15: A silver-stained SDS-PAGE gel showing the protein content of the virus preparation following different steps of the process of the invention (defined in the table next to the figure). The SGC purified pool consisting of SGC fractions F7-F11 is shown in lane 12.

Figure 16: The SEC area (mAU*min; right axis) and TCID₅₀ results (log TCID₅₀/mL; left axis) of ChikV production harvests before and after PS treatment is shown. The grey portions of the bars indicate large losses in SEC area following PS treatment, but no corresponding change in the total number of infectious particles (indicated by black portions of the bars) (A); SEC profile of virus preparation before and after PS addition, showing a complete removal of large size virus aggregates by PS treatment as well as a reduction in host cell proteins (HCP) and LMW impurities (B).

Figure 17: Relative amounts of ChikV particles and other components by SEC-HPLC analysis at the different steps of the process of the invention including, from top to bottom: crude harvest (a) are shown; 10X concentrated harvest; diafiltrated harvest; PS treated material; CC700-treated material and SGC purified pool.

Figure 18: Comparison of different sucrose gradients (a: gradient 1: 50%, 10% sucrose, b gradient 2: 50%, 35%, 10% sucrose, c: gradient 3: 50%, 25%, 10% sucrose, d: gradient 4: 50%, 35%, 15%, 10% sucrose) with ChikV particles.

Figure 19: Comparison of two different ZikaV harvest schedules.

Figure 20: SEC-HPLC elution profile of ZikaV NIV. Data were processed on Dionex Ultimate 3000 / Superose 6 Increase column.

Figure 21: SEC-MALLS analysis of inactivated ZikaV.

Figure 22: Cumulative particle size distribution of Zika NIV.

DETAILED DESCRIPTION OF THE INVENTION

Disclosed herein are virus vaccines and compositions comprising an inactivated virus, and related methods of producing said vaccines and compositions. Also provided are methods of administering said virus vaccines for the prevention of virus infection and/or for the production of an anti-virus immune response in subjects, for example subjects at risk of

being exposed to virus. In particular, the invention is directed to a virus vaccine comprising an optimally inactivated virus particle, wherein the virus particle in an appropriate dose is able to seroconvert a subject that is administered the virus vaccine with at least a 70% probability, preferably an 80% probability. Another advantage of the invention is that related methods of producing said vaccines and compositions are very efficient and provide pure compositions largely void of impurities, in particular protamine sulphate, allowing for high volume production of vaccines. Examples to the above are provided for Zika virus and Chikungunya virus.

Disclosed herein are downstream processes for purifying virus particles from a crude preparation. The downstream process can be applied to either a virus which has not adapted for propagation on a particular cell substrate or for a partial / fully cell substrate adapted virus particle.

Aspects of the invention provide processes for the purification of infectious virus particles comprising the steps of (a) providing a crude harvest (a) comprising virus particles and impurities, wherein the impurities are generated from growing said virus particles on a cell substrate; (b) reducing impurities from the crude harvest (a) by precipitation with an agent comprising a protamine salt, preferably a protamine sulphate, to obtain a virus preparation (b); and further purifying the virus preparation (b) by an optimized sucrose density gradient centrifugation to obtain a virus preparation (c) comprising the infectious virus particles.

In some embodiments, the concentration of protamine sulphate in step (b) is about 1 to 10 mg/ml, more preferably about 1 to 5 mg/ml, more preferably about 1 to 2 mg/ml. In one embodiment, the concentration of protamine sulphate in step (b) is about 2 mg/mL. In one embodiment, the concentration of protamine sulphate is 1.2 to 1.8 mg/ml, more preferably 1.4 to 1.6 mg/ml. In a preferred embodiment, the concentration of protamine sulphate in step (b) is about 1.6 mg/ml (for e.g. Chikungunya) or about 2 mg/ml (for e.g. Zika).

In some embodiments, the residual host cell DNA of the virus preparation (c) is less than 1 µg/mL, especially less than 900, 800, 700, 600, 500, 400, 300 or 200 ng/mL, preferably less than 100 ng/mL. In a preferred embodiment, the residual host cell DNA of the virus preparation (c) is less than 10 ng/mL. In some embodiments, the residual host cell protein of the final virus preparation (c) is less than 10 µg/mL, especially less than 9, 8, 7, 6, 5, 4, 3 or 2 µg/mL, preferably less than 1 µg/mL. In a preferred embodiment, the residual

host cell protein of the virus preparation (c) is less than 100 ng/mL. In some embodiments, the residual non-infectious virus particles of the final virus preparation (c) is less than 10 µg/mL, especially less than 9, 8, 7, 6, 5, 4, 3 or 2 µg/mL, preferably less than 1 µg/mL. In a preferred embodiment, the residual non-infectious virus particles of the virus preparation (c) is less than 100 ng/mL. In some embodiments, the residual protamine is less than 1 µg/mL, especially less than 900, 800, 700, 600, 500, 400, 300 or 200 ng/mL, preferably less than 100 ng/mL, more preferably is below the detection limit in particular below the detection limit in the final drug substance.

In some embodiments, the crude harvest (a) comprising the virus particles and impurities is subjected to one or more pre-purification step(s) prior to step (b). In some embodiments, the one or more pre-purification step(s) comprises digesting host cell genomic DNA in the crude harvest (a) comprising the virus particles and impurities by enzymatic treatment. In some embodiments, the one or more pre-purification step(s) comprises filtration, ultrafiltration, concentration, buffer exchange and/or diafiltration. In some embodiments, the one or more pre-purification steps is filtration using a filter having a pore size equal to or less than 1 µm. In some embodiments, the filter has a pore size equal to or less than 0.2 µm. In a preferred embodiment, the filter has a pore size of 0.2 µm. In some embodiments, the concentration and/or ultra/diafiltration and/or buffer exchange is performed by tangential flow filtration (TFF). In some embodiments, ultra/diafiltration of the crude harvest (a) comprising the virus particles and impurities is performed using a hollow fiber membrane having a cut-off of equal to or less than 300 kDa. In a preferred embodiment, the hollow fiber membrane has a cut-off of 100 kDa.

In some embodiments, the virus particle is a live virus, a chimeric virus, an attenuated live virus, a modified live virus, or a recombinant live virus. In a further step, the virus particles of the invention may be optionally inactivated. In some embodiments, the virus particle is an attenuated form of the virus particle. For example, the virus may have reduced infectivity, virulence, and/or replication in a host, as compared to a wild-type virus. In some embodiments, the virus is a mutated or modified virus, for example the nucleic acid of the virus may contain at least one mutation relative to the wild-type virus. In some embodiments, the virus is a recombinant live virus, meaning a virus that is generated recombinantly and may contain nucleic acid from different sources.

In some embodiments, the virus particle is a live virus, an attenuated live virus, a modified live virus, or a recombinant live virus. In some embodiments, the virus belongs to a virus family selected from the group consisting of Paramyxoviridae, Orthomyxoviridae, Flaviviridae, Filoviridae, Arenaviridae, Rhabdoviridae, and Coronaviridae. In some
5 embodiments, the virus belongs to a virus family selected from the group consisting of
Togaviridae (being live or inactivated), such as alphaviruses, or Flaviviridae (being live or
inactivated). In some embodiments, the virus is a virus of the family Flaviviridae, i.e. a
flavivirus. In other embodiments, the virus is a Zika virus or Yellow Fever virus. In
preferred embodiments, the virus is a Zika virus. In a most preferred embodiment, the Zika
10 virus is a Zika virus from the Asian lineage.

In some embodiments, the relative reduction of impurity of the final virus preparation
relative to the liquid medium (a) comprising the virus particles and impurities is in a range
from 60 to 95%. In some embodiments, the residual impurity of the final virus preparation is
less than 1%.

15 In some embodiments, the filtration of step in (b)(ii) of claim 1 is performed using a
filter having a pore size equal to or greater than 1 μm . In some embodiments, the filter has a
pore size equal to or greater than 0.2 μm . In a preferred embodiment, the filter has a pore
size of 0.2 μm .

In some embodiments, the virus is propagated in a cell line selected from the group
20 consisting of an EB66 cell line, a Vero cell line, a Vero- α His cell line, a HeLa cell line, a
HeLa-S3 cell line, a 293 cell line, a PC12 cell line, a CHO cell line, a 3T3 cell line, a PerC6
cell line, a MDSK cell line, a chicken embryonic fibroblast cell line, a duck cell line, and a
diploid avian cell line. In some embodiments, said cell line is a duck cell line. In some
embodiments, said cell line is a diploid avian cell line. In some embodiments, said cell line is
25 EB66 cell line. In a preferred embodiment, said cell line is a Vero cell line.

Aspects of the invention provide a use of any of the processes described herein for
manufacturing a composition for immunization against a viral infection. In a preferred
embodiment, the composition is a vaccine. In one embodiment, the composition or vaccine is
directed against Chikungunya virus. In one embodiment, the composition or vaccine is
30 directed against a flavivirus. In one embodiment, the composition or vaccine is directed
against Yellow Fever virus. In one embodiment, the composition or vaccine is directed
against Zika virus such as e.g. a Zika virus of the Asian lineage.

Other aspects provide compositions comprising the virus particles obtainable by any of the processes described herein for treating and/or preventing a viral infection. In one embodiment, the viral infection is caused by Chikungunya virus. In one embodiment, the viral infection is caused by a flavivirus. In one embodiment, the viral infection is caused by Yellow Fever virus. In one embodiment, the viral infection is caused by Zika virus such as e.g. a Zika virus of the Asian lineage.

Furthermore, disclosed herein are Zika virus vaccines and compositions comprising an inactivated Zika virus, and related methods of producing said vaccines and compositions. Also provided are methods of administering the Zika virus vaccines for the prevention of Zika virus infection and/or for the production of an anti-Zika virus immune response in subjects, for example subjects at risk of being exposed to Zika virus.

Zika virus is a flavivirus closely related to Dengue virus and is similarly transmitted by the *Aedes* species mosquito, although other arthropod vectors for Zika virus are possible. Since it was first isolated from a Rhesus monkey in the Zika forest of Uganda in 1947, there were very few reported incidents of human infection, especially outside of the endemic regions of Africa and Asia until a large outbreak in French Polynesia in 2007 (Haddow *et al. PLoS Neglected Tropical Diseases* (2012) 6(2), Malone *et al. PLoS Neglected Tropical Diseases* (2016) 10(3),). The virus has since spread through islands of the Pacific, including Oceania, and into South and Central America (WHO “Zika Situation Report” February 5, 2016).

In addition to being spread by the bite of an infected mosquito, evidence also suggests transmission may occur between individuals, such as from the blood of an infected individual, *in utero*/transplacental transmission from an infected mother to the fetus, sexual transmission between sexual partners, and possibly by other local transmission routes. There is a possible association between Zika virus infection during pregnancy and microcephaly in the fetus/neonate. Microcephaly is a rare condition in which a baby’s head circumference is significantly less than expected based on the average for their age, sex, and ethnicity. This is a result of the brain failing to undergo proper embryonic development, and in 90% of cases is associated with mental retardation (Rocha *et al. (2016) Bull World Health Organ* 8 Feb. 2016).

There is a probable association between individuals having had a prior Zika virus infection and the incidence of Guillain-Barré syndrome, a neurological disorder in which the

individual's immune system destroys the myelin sheath surrounding axons of the peripheral nervous system (WHO "Zika Situation Report" February 5, 2016).

No specific treatments or vaccines for Zika virus currently exist, and the only measures at this time to prevent infection are through vector control and avoiding travel to regions experiencing outbreaks.

Described herein are Zika virus vaccines and compositions comprising inactivated Zika virus that provide a safe method for generating an immune response to Zika virus, including virus-neutralizing antibodies, that may help prevent against Zika virus infection.

Any strain of Zika virus may be used in the methods and compositions described herein. In some embodiments, the Zika virus is an isolate from an infected subject during a Zika virus outbreak. In some embodiments, the Zika virus is a strain isolated from Africa or from the African virus lineage. In some embodiments, the Zika virus is a strain isolated from Asia or from the Asian lineage (includes also strains from French Polynesia). In some embodiments, the Zika virus is a strain isolated from the Americas (South America, Central America, or North America), such as a Suriname Zika virus strain. In some embodiments, the Zika virus has a RNA genome corresponding (but not limited) to the DNA sequence provided by GenBank Accession No. AY632535.2, KU321639.1, KU497555.1, KU501215.1, KU509998.1, KU527068.1, KU681081.3, KU681082.3, KU707826.1, KU744693.1, or LC002520.1 or RNA genome disclosed partially or fully herein (SEQ ID NO: 2 to 69).

In some embodiments, the attenuated form of ChikV is derived from the LR2006-OPY1 ChikV infectious clone (La Reunion isolate). In some embodiments, the attenuated form of ChikV is the $\Delta 5\text{nsP3}$ mutant as described by Hallengård et al. (Novel Attenuated Chikungunya Vaccine Candidates Elicit Protective Immunity in C57BL/6 mice (2014) Journal of Virology 88(5):2858–2866) or an immunogenic variant thereof. The immunogenic variant of the $\Delta 5\text{nsP3}$ ChikV mutant is herein defined as having at least 80% sequence identity to the nucleotide sequence of the $\Delta 5\text{nsP3}$ mutant sequence, especially at least 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or at least 99% sequence identity.

In some embodiments, the process of the invention results in an enrichment of infectious virus particles from the crude harvest comprising infectious virus particles and non-infectious virus particles and other virus products such that the enrichment of the

infectious virus particles is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, preferably at least 80%, especially 85% relative to the total virus particle content of the crude harvest (a) comprising the virus particles and impurities.

In some embodiments, the residual impurity of the final virus preparation with respect to all impurities in the crude harvest is less than 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, preferably less than 5% as determined by SEC-HPLC (Size Exclusion Chromatography – HPLC).

Another aspect of this invention is the realization that by using an approach of a type of vaccine (i.e. the Japanese Encephalitis Vaccine (JEV) with tradename IXIARO®, see Srivastava A.K. et al., 2001, Vaccine 19, 4557-4565, WO99/11762) which the regulatory agencies have seen and licensed before, it may be possible to very quickly develop a Zika or Chikungunya vaccine and provide it to the subjects in need as soon as possible. The industrial process as disclosed for IXIARO®, providing a very effective vaccine against JEV, had to be complemented by further inventions disclosed herein in order to provide a more efficient (higher yield) and safer (less or no protamine sulphate with its allergic potential) Zika vaccine compared to the available JEV vaccine. A particular innovation of the herein disclosed vaccines are their avoidance of any protamine salt (SEQ ID NO: 1) in the final drug substance by introducing an improved sucrose gradient. Said sucrose gradient not only allowed the separation of protamine sulphate but also allowed for a very effective inactivation by formaldehyde and resulted in the case of Zika with over 90% yield with the improved process disclosed herein vs about 35% yield with the published JEV process, see experimental part for comparison).

Aspects of the disclosure relate to methods of producing a virus in Vero tissue culture cells. Vero cells are a commonly used tissue culture cell line derived from the kidney of an African green monkey. The Vero cells used in the methods described herein are the VERO (WHO) cell line, obtained from the Health Protection Agency general cell collection under catalogue number 88020401.

Vero cells can be grown to confluent monolayers, for example in tissue culture flasks; in suspension (on microcarriers), for example in roller bottles; or in any other cell culture system for viral production. In some embodiments, the Vero cells are grown in a bioreactor for viral production. For plaque assays or plaque reduction neutralization test (PRNT), Vero cells are grown in monolayers in tissue culture flasks, dishes, or wells of a plate. To infect

the Vero cells with the virus, the culture medium is inoculated with virus and the cells are incubated with the virus for a period of time. The cells may be washed after inoculation to remove any virus that did not adsorb to the cells in a given amount of time.

The methods provided herein involve passaging the virus in Vero cells. As used herein, the terms “passage” or “passaging” refer to infecting a population of Vero cells with virus and subsequently inoculating a second population of Vero cells with virus produced by infection of the first Vero cell population. In some embodiments, a portion of the culture medium from the infected Vero cells (containing virus that was released from the infected cells) is used to inoculate a second population of Vero cells. This is referred to as one passage or one round of passaging. The passaging may be performed serially, for example, a portion of the culture medium from the infected second population of Vero cells is used to inoculate a third population of Vero cells, and so on. In some embodiments, virus obtained from a single plaque is used to inoculate another population of cells.

In some embodiments, the virus is passaged in Vero cells several times, such as at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 times. In some embodiments, the virus is passaged in Vero cells at least 4 times or 5 times. In some embodiments, the virus is passaged in Vero cells at least 30 times. It is important that the virus population, i.e. the virus sequences, stays as much as possible constant over said passaging. If adaption of the virus occurs (i.e. appearance of mutated viruses in the original virus population), it is preferred that said passages are not used in the context of manufacturing of said virus, e.g. for Zika it was found that up to passage 3 and culturing to day 7 can be used without major shifts in virus population, i.e. introduction of virus population with mutations. However this observation need to be done for each virus strain and may be different.

In some embodiments, the Vero cells are incubated for at least 2 days after inoculation with the virus at e.g. a typical 0,01 MOI (multiplicity of infection), to allow for viral production, prior to passaging. In some embodiments, the Vero cells are incubated for at least 3, 4, 5, 6, 7, 8, 9, 10 or more than 10 days e.g. at least 7 days after inoculation with the virus prior to passaging. The number of days the Vero cells are incubated after viral inoculation may depend on factors such as the multiplicity of infection used to inoculate the cells and the viral titer desired in the culture medium. Serial passaging of the virus in Vero cells may result in generation of a Vero cell adapted virus strain.

The culture medium from the infected Vero cells may be harvested (collected) to obtain the virus. In some embodiments, the culture medium is harvested from infected Vero cells and is replaced with fresh culture medium, which is then harvested after another period of time. In some embodiments, the culture medium harvested from infected Vero cells is
5 pooled from independent Vero cell cultures and/or from independent days. Harvesting can be repeated up to 4 times by 7 or 9 days post infection, for example, and result in a high yield of virus per unit cell culture. In order to minimize the adoption of Zika virus strain to Vero cells, it was found that Vero cell could be incubated for at least 7 days, more preferably 5 days, prior to passaging and subsequently supernatants could be harvested at days 2, 3, 5 and 7 or
10 2, 3, and 5 (see also experimental part). The harvested culture medium can be stored at +4°C prior to purification of the virus from the culture medium up to 2 weeks.

In some embodiments, debris from infected and lysed Vero cells may be removed from the harvested culture medium, referred to as a “clarification” of the culture medium. The harvested culture medium may be clarified by common methods known in the art, such
15 as low-speed centrifugation, for example, at 1500 *g* for 10 min, and/or by filtration through a filter of pore size of 0.45 μm . The harvested culture medium can be stored at +4°C prior to concentration.

To concentrate the titer of the virus in the harvested culture medium, it may be subjected to concentration by any method known in the art. For example, the harvested
20 culture medium may be concentrated by methods including, without limitation, ultrafiltration, ultracentrifugation, centrifugal concentrator, vacuum centrifugation, and lyophilization. In some embodiments, the harvested culture medium is concentrated by ultrafiltration and the retentate containing the Zika virus is collected. In some embodiments, the harvested culture medium is concentrated by precipitation in which polyethylene glycol (PEG) 8000 is
25 dissolved in the culture medium (up to 10%) and the precipitate is dissolved in a buffer, for example phosphate-buffered saline (PBS, pH 7.0).

The harvested culture medium may be precipitated to produce a virus supernatant. In some embodiments, the harvested culture medium is precipitated to remove Vero cell DNA and other undesired material, such as Vero cell debris, from the harvested culture medium. In
30 some embodiments, the harvested culture medium is concentrated prior to precipitation. In some embodiments, the harvested culture medium is precipitated by adding protamine sulfate (e.g. SEQ ID NO: 1) to the harvested culture medium and incubating the mixture, for

example at +4°C or on ice. In some embodiments, the harvested culture medium is treated with benzonase to remove Vero cell DNA and other undesired material, such as Vero cell debris, from the harvested culture medium. However, it was found that the treatment with protamine sulfate is preferred (see experimental part). In some embodiments, the precipitated culture medium is centrifuged to collect precipitated material and the supernatant containing the virus, referred to as a “virus supernatant,” is collected.

The virus supernatant may be further purified after precipitation, for example density gradient ultracentrifugation. In some embodiments, the virus supernatant is further purified by sucrose gradient. Fractions may be collected from the sucrose gradients and assayed for presence of the virus. Methods for assaying for virus positive fractions include plaque assay, hemagglutination assay, polyacrylamide gel electrophoresis, and antigen assays such as Western blotting and ELISA's. The fractions containing virus may be pooled based on titer of the virus and level of other impurities. The level or amount of impurities present in the virus supernatant can be estimated by testing for Vero cell DNA, virus aggregates and/or Vero cell protein (see experimental part). A particular embodiment of the invention is the improved sucrose gradient that allows for an efficient protamine separation as shown in experimental part. It was surprisingly found that addition of a 10% sucrose virus containing fraction to a simple three layer sucrose density gradient (e.g. a gradient comprising a 15% (w/w) sucrose solution, a 35% (w/w) sucrose solution, and a 50% (w/w) sucrose solution) was able to efficiently separate protamine sulphate without much loss of virus. Thus a particularly preferred embodiment of the invention is the use of a sucrose density gradient that is able to efficiently separate protamine sulphate, wherein said sucrose density gradient is used in the purification of virus such as the viruses described herein, e.g. a Zika virus, Yellow Fever virus or Chikungunya virus.

To achieve a safe vaccine or composition for the administration to subjects, the virus supernatant may be inactivated (see experimental part for Zika virus). As used herein, the terms “inactivated” and “optimally inactivated” may be used interchangeably and refer to a process (or its result) by which the virus is rendered unable to infect a host cell (non-infectious), but that does not affect or substantially affect the antigenicity of the virus, for example, the immunogenic antigens exposed on the surface of the virus are able to stimulate an immune response in a subject (*e.g.*, antigen-specific antibodies). By “does not affect or substantially affect the antigenicity of the virus” is meant that the inactivated virus retains at

least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or even essentially 100% of the antigenicity of a virus that is not subjected to inactivation.

A variety of methods are known in the art for inactivating viruses. In some
 5 embodiments, the virus is inactivated by chemical inactivation, thermal inactivation, pH inactivation, or UV inactivation.

In some embodiments, the inactivating is by chemical inactivation and involves contacting the virus with one or more chemical inactivation agent for a period of time under conditions such that the virus is inactivated but the antigenic epitopes are substantially intact.

10 In some embodiments, the virus is inactivated for a period of time that is longer than is required to completely inactivate the virus. In some embodiments, the virus supernatant is inactivated for the number of days required to inactivate the virus plus at least one additional day. Samples of the virus supernatant may be taken at one or more times throughout the inactivation process and assessed for viral viability (infectivity) by any method known in the
 15 art, such as by infecting a monolayer of host cells (*i.e.*, plaque assay). Using such a procedure, the period of time that is required to completely inactivate the virus can be determined, and a longer period of time is selected to ensure complete inactivation.

In some embodiments, the virus is contacted with a chemical inactivation agent for between 1 day and 50 days, between 2 days and 40 days, between 2 days and 30 days,
 20 between 2 days and 20 days, between 2 days and 10 days, between 3 days and 9 days, between 4 days and 8 days, between 5 days and 7 days, between 2 days and 5 days, or between 5 and 10 days. In some embodiments, the virus is contacted with one or more chemical inactivation agents for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18
 25 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, 32 days, 33 days, 34 days, 35 days, 36 days, 37 days, 38 days, 39 days, 40 days, 41 days, 42 days, 43 days, 44 days, 45 days, 46 days, 47 days, 48 days, 49 days, or at least 50 days.

In some embodiments, the chemical inactivation is performed at about +5°C, +10°C,
 30 +15°C, +20°C, +25°C, +30°C, +35°C, +40°C, or about +45°C. In some embodiments, the chemical inactivation is performed at about +4°C. In some embodiments, the chemical inactivation is performed at about +22°C.

Any chemical inactivation agent known in the art may be suitable for inactivating the virus in the methods described herein. It will be appreciated by one of skill in the art that factors such as the chemical inactivation agent and the temperature at which inactivation is performed may affect the length of time (number of days) required to completely inactivate the virus. Examples of chemical inactivation agents include, without limitation, formaldehyde, enzymes, β -propiolactone, ethanol, trifluoroacetic acid, acetonitrile, bleach, urea, guanidine hydrochloride, tri-n-butyl phosphate, ethylene-imine or a derivatives thereof, and organic solvents such as Tween, Triton, sodium deoxycholate, and sulphohetain. A preferred inactivation is the inactivation with formaldehyde at 22°C +/-2°C for about 10 days.

In some embodiments, the inactivating agent is neutralized after chemical inactivation of the virus. In some embodiments, the inactivating agent is formaldehyde and is neutralized after chemical inactivation using sodium thiosulphate or sodium metabisulfite.

In some embodiments, the virus is inactivated by thermal inactivation. In some embodiments, the thermal inactivation involves exposing the virus to heat, such as dry heat or vapor heat, for a period of time. In some embodiments, the thermal inactivation involves exposing the virus to temperatures of about +40°C, +45°C, +50°C, +55°C, +60°C, +65°C, +70°C, +75°C, +80°C, +85°C, +90°C, +95°C, or about +100°C. In some embodiments, the virus is exposed to heat for at least 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, 84 hours, about 96 hours, or longer. A preferred thermal inactivation involves exposing the virus to temperatures of about +56°C for 60 minutes.

In some embodiments, the virus is inactivated by exposing the virus to acidic or alkaline conditions for a period of time such that the virus is completely inactivated. The pH of a virus preparation may be adjusted to a desired pH, for example by the addition of an acid, a base, or a buffer with a particular pH to the virus preparation. In some embodiments, the virus is inactivated at an acidic pH of about 2, 2.5, 3, 3.5, 4, 4.5, 5 or about 5.5. In other embodiments, the virus is inactivated at an alkaline pH of about 8, 8.5, 9, 9.5, 10, or about 10.5.

In some embodiments, the virus is inactivated using UV inactivation. UV inactivation involves exposing the virus to energy-rich radiation, such as UV-A, UV-B, or UV-C light for a period of time.

It will be appreciated that any two or more methods of inactivation may be combined and performed concurrently or serially.

The inactivated virus may be subsequently dialyzed to remove any undesired material, including the inactivating agent and any neutralizing agent, and/or to replace the buffer with a buffer that is pharmaceutically acceptable for administration to subjects. In some embodiments, the inactivated virus is dialyzed with PBS. In addition or alternatively, the inactivated virus may be filtered, such as sterile filtered, through a 0.22 μm filter.

It is believed that the herein described improved process (comprising the PS treatment in combination with the optimized sucrose gradient) is applicable and efficient to any virus purification and in particular efficient for any RNA type virus (such as the herein described Zika and Chikungunya and yellow fever viruses) of similar size (i.e. about 50 to 100 nm). Furthermore, it is believed that the combination of the PS treatment with the optimized sucrose gradient (allowing for a complete (or almost complete) separation of PS provides a very efficient virus purification in the very high range, e.g. above 70%, more preferably 75%, 80% or 90%, even more preferably 95%. It is believed that the complete reduction of PS in the virus fraction through the process of the invention allows a very efficient inactivation with almost no or very low viral loss e.g. below 30%, more preferably less than 25%, 20% or 10% loss, even more preferably less than 15% loss.

Any of the methods or uses described herein may be for the prevention of a virus infection in a subject. As used herein, the terms “prevent,” and “preventing,” include the administration of a virus vaccine or composition to a subject to reduce, or delay the onset of the manifestation of clinical or subclinical symptoms, complications, pathologies or biochemical indicia of a disease or infection, or to reduce or inhibit the spread/transmission of the virus. As used herein, antigen(s), such as an inactivated virus, that is administered to a subject prophylactically (e.g., prior to infection) may be referred to as a vaccine.

Zika Vaccine

As described herein Zika virus may cause any of a variety of symptoms upon infection of a subject, and is generally characterized by mild fever; rash (exanthema) on face, neck trunk, upper arms; headache; sensitivity to light; non-inflammatory joint pain; conjunctivitis; lack of appetite; diarrhea; abdominal pain; and/or dizziness. Zika virus infection during pregnancy is likely associated with microcephaly in the fetus/neonate. There

is also a probable association between the onset of Guillain-Barré syndrome or symptoms thereof. Diagnosis of Zika virus infection in subjects exposed to Zika virus or suspected of being exposed to Zika virus involves detecting the presence of virus-specific antibodies and/or molecular testing, such as PCR or real-time PCR detection of Zika virus.

5 Provided herein are methods for administering a dose of a therapeutically effective amount of a Zika virus vaccine to a subject in need thereof. In some embodiments, the subject is a mammalian subject, such as a human, non-human primate, rodent, rabbit, sheep, dog, cat, horse, or cow. In some embodiments, the subject is a mouse. In some
10 embodiments, the subject is a human subject, such as a child, an adult, or an elderly adult. In some embodiments, the subject is a female subject. In some embodiments, the subject is pregnant or planning on becoming pregnant. In some embodiments, the subject is at risk of being exposed to Zika virus. In some embodiments, the subject is living in or traveling to an area where Zika virus is present or is thought to be present. In some embodiments, the subject is living in or traveling to an area that is experiencing a Zika virus infection outbreak.
15 In some embodiments, the subject is living in or traveling to an area where an arthropod vector capable of transmitting the Zika virus vector is present or is thought to be present.

Any of the Zika virus vaccines or compositions described herein may be administered to a subject in a therapeutically effective amount or a dose of a therapeutically effective amount. As used herein, a “therapeutically effective amount” of vaccine is any amount that
20 results in a desired response or outcome in a subject, such as those described herein, including but not limited to prevention of infection, an immune response or an enhanced immune response to Zika virus, or prevention or reduction of symptoms associated with Zika disease.

In some embodiments, the therapeutically effective amount of a Zika virus vaccine or
25 composition described herein is an amount sufficient to generate antigen-specific antibodies (*e.g.*, anti-Zika virus antibodies). In some embodiments, the therapeutically effective amount is sufficient to seroconvert a subject with at least 70% probability. In some embodiments, the therapeutically effective amount is sufficient to seroconvert a subject with at least 75%, 80%, 85% 90%, 95%, 96%, 97%, 98%, or at least 99% probability. Whether a subject has been
30 seroconverted can be assessed by any method known in the art, such as obtaining a serum sample from the subject and performing an assay to detect anti-Zika virus antibodies. In some embodiments, a subject is seroconverted if a serum sample from the subject contains an

amount of anti-Zika virus antibodies that surpasses a threshold or predetermined baseline. A subject is generally considered seroconverted if there is at least a 4-fold increase in anti-Zika virus antibodies (*i.e.*, anti-Zika E protein IgG antibodies) present in a serum sample from the subject as compared to a serum sample previously taken from the same subject.

5 In some embodiments, seroconversion of a subject is assessed by performing a plaque reduction neutralization test (PRNT). Briefly, PRNT is used to determine the serum titer required to reduce the number of Zika virus plaques by 50% (PRNT50) as compared to a control serum/antibody. The PRNT50 may be carried out using monolayers of Vero cells or any other cell type/line that can be infected with Zika virus. Sera from subjects are diluted
10 and incubated with live, non-inactivated Zika virus. The serum/virus mixture may be applied to the Vero cells and incubated for a period of time. Plaques formed on the Vero cell monolayers are counted and compared to the number of plaques formed by the Zika virus in the absence of serum or a control antibody. A threshold of neutralizing antibodies of 1:10 dilution of serum in a PRNT50 is generally accepted as evidence of protection (Hombach *et al.* Vaccine (2005) 23:5205-5211).

15 In some embodiments, the Zika virus may be formulated for administration in a composition, such as a pharmaceutical composition. The term “pharmaceutical composition” as used herein means a product that results from the mixing or combining of at least one active ingredient, such as an inactivated Zika virus, and one or more inactive ingredients,
20 which may include one or more pharmaceutically acceptable excipient.

Pharmaceutical compositions of the invention, including vaccines, can be prepared in accordance with methods well known and routinely practiced in the art (see *e.g.*, Remington: The Science and Practice of Pharmacy, Mack Publishing Co. 20th ed. 2000; and Ingredients of Vaccines – Fact Sheet from the Centers for Disease Control and Prevention, *e.g.*, adjuvants
25 and enhancers such as alum to help the vaccine improve its work, preservatives and stabilizers to help the vaccine remain unchanged (*e.g.*, albumin, phenols, glycine)). Pharmaceutical compositions are preferably manufactured under GMP conditions. Typically a therapeutically effective dose of the inactivated Zika virus preparation is employed in the pharmaceutical composition of the invention. The inactivated Zika virus is formulated into
30 pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art. Dosage regimens are adjusted to provide the optimum desired response (*e.g.*, the prophylactic response).

Dosages of the active ingredients in the pharmaceutical compositions of the present invention can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired pharmaceutical response for a particular subject, composition, and mode of administration, without being toxic to the subject. The selected dosage level depends upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the subject being treated, and like factors.

A physician, veterinarian or other trained practitioner, can start doses of the inactivated Zika virus vaccine employed in the pharmaceutical composition at levels lower than that required to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect (*e.g.*, production of anti-Zika virus antibodies) is achieved. In general, effective doses of the compositions of the present invention, for the prophylactic treatment of groups of people as described herein vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and the titer of anti-Zika virus antibodies desired. Dosages need to be titrated to optimize safety and efficacy. In some embodiments, the dosing regimen entails subcutaneous or intramuscular administration of a dose of inactivated Zika virus twice, once at day 0 and once at about day 7. In some embodiments, the dosing regimen entails subcutaneous administration of a dose of inactivated Zika virus twice, once at day 0 and once at about day 14. In some embodiments, the dosing regimen entails subcutaneous administration of a dose of inactivated Zika virus twice, once at day 0 and once at about day 28. In some embodiments, the inactivated Zika virus is administered to the subject once.

Any of the Zika virus vaccines or compositions described herein may be administered to a subject with, prior to, or after administration of one or more adjuvants. An adjuvant is a molecule that enhances a response in a subject, such as an immune response, to an antigen or other molecule. In some embodiments, an adjuvant may stabilize an antigen or other molecule. Determining whether a Zika virus vaccine or compositions thereof are administered with an adjuvant depends on various factors (*e.g.*, type and extent of response

desired) and will be evident to one of skill in the art. In some embodiments, administering any of the Zika virus vaccines or compositions described herein with, prior to, or after administration of an adjuvant may enhance the production of virus neutralizing (anti-Zika virus) antibodies. In some embodiments, a subject that is administered any of the Zika virus vaccines or compositions described herein with, prior to, or after administration of an adjuvant may only require a single administration of the Zika virus vaccine or composition to be seroconverted (produce a level of anti-Zika virus antibodies). Examples of adjuvants may include, without limitation, aluminium salt (aluminium hydroxide or aluminium phosphate), calcium phosphate hydroxide, paraffin oil, killed bacteria, bacterial toxins, toxoids, subunits of bacteria, squalene, thimerosal, detergents, IL-1, IL-2, IL-12, 2-component adjuvants, such as 2-component adjuvants containing an antibacterial peptide and a TLR9 agonist (*e.g.*, IC31®), and combinations such as Freund's complete adjuvant and Freund's incomplete adjuvant. In some embodiments, the Zika virus vaccines or compositions is administered with aluminium hydroxide. In some embodiments, the inactivated Zika virus vaccine or composition is administered with aluminium phosphate salt. A preferred aluminium salt is the aluminium hydroxide with reduced Cu content, *e.g.* lower than 1,25ppb based on the weight of the Zika composition, an adjuvant described in detail in WO 2013/083726 or Schlegl et al., Vaccine 33 (2015) 5989-5996.

In some embodiments, the adjuvant is comprised of two components. In some embodiments, the 2-component adjuvant comprises an antibacterial peptide and a TLR9 agonist. In some embodiments, the antibacterial peptide is provided by the amino acid sequence KLKL₅KLK (SEQ ID NO: 70). In some embodiments, the TLR9 agonist is a deoxyinosine-containing immunostimulatory oligodeoxynucleic acid molecule (I-ODN). In some embodiments, the I-ODN comprises the nucleic acid sequence (dIdC)₁₃ (SEQ ID NO: 69). In some embodiments, the adjuvant is IC31®. In some embodiments, the adjuvant is in nanoparticle form (See, *e.g.*, US Patent No. 8,765,148 B2, incorporated by reference in its entirety). In some embodiments, the adjuvant is IC31®, *i.e.* KLKL₅KLK (SEQ ID NO: 71) and the nucleic acid sequence (dIdC)₁₃ (SEQ ID NO: 72), in combination with an aluminium salt such as aluminium hydroxide.

The Zika virus vaccines or compositions described herein may be administered to a subject concomitantly with one or more vaccine to another infectious agent, such as another infectious agent is that present or thought to be present in the same geographic area as Zika

virus. In some embodiments, the other infectious agent is one that the subject is also at risk of being in contact with. In some embodiments, the other infectious agent is transmitted by the same arthropod vector as Zika virus. In some embodiments, the other infectious agent is Japanese Encephalitis virus, Yellow Fever virus, Dengue virus and/or Chikungunya virus.

5 Also within the scope of the present disclosure are kits for use in prophylactically administering to a subject, for example to prevent or reduce the severity of Zika virus infection. Such kits can include one or more containers comprising a composition containing inactivated Zika virus, such as an inactivated Zika virus vaccine. In some embodiments, the kit may further include one or more additional containing comprising a second composition,
10 such as a second vaccine. In some embodiments, the second vaccine is a vaccine for another arbovirus. In some embodiments, the second vaccine is a Dengue virus vaccine and/or a Chikungunya virus vaccine.

 In some embodiments, the kit can comprise instructions for use in accordance with any of the methods described herein. The included instructions can comprise a description of
15 administration of the composition containing inactivated Zika virus to prevent, delay the onset, or reduce the severity of Zika virus infection. The kit may further comprise a description of selecting a subject suitable for administration based on identifying whether that subject is at risk for exposure to Zika virus or contracting a Zika virus infection. In still other embodiments, the instructions comprise a description of administering a composition
20 containing inactivated Zika virus to a subject at risk of exposure to Zika virus or contracting Zika virus infection.

 The instructions relating to the use of the composition containing inactivated Zika virus generally include information as to the dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages
25 (e.g., multi-dose packages) or sub-unit doses. Instructions supplied in the kits of the invention are typically written instructions on a label or package insert (e.g., a paper sheet included in the kit), but machine readable instructions are also acceptable.

 The kits of the present disclosure are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging, and the like. Also
30 contemplated are packages for use in combination with a specific device, such as a syringe or an infusion device. The container may have a sterile access port, for example the container

may be a vial having a stopper pierceable by a hypodermic injection needle. At least one active agent in the composition is an inactivated Zika virus, as described herein.

This invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of “including,” “comprising,” or “having,” “containing,” “involving,” and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The methods and techniques of the present disclosure are generally performed according to conventional methods well-known in the art. Generally, nomenclatures used in connection with, and techniques of biochemistry, enzymology, molecular and cellular biology, microbiology, virology, cell or tissue culture, genetics and protein and nucleic chemistry described herein are those well-known and commonly used in the art. The methods and techniques of the present disclosure are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated.

The present invention is further illustrated by the following examples, which in no way should be construed as further limiting. The entire contents of all of the references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated by reference, in particular for the teaching that is referenced hereinabove. However, the citation of any reference is not intended to be an admission that the reference is prior art.

SEQUENCES

The amino acid sequence of a typical form of protamine is provided by SEQ ID NO: 1: PRRRRSSSRP VRRRRRPRVS RRRRRRGGRR RR.

Provided below are examples of nucleic acid sequences of the genomes of Zika viruses that may be used in the methods, compositions, and/or vaccines described herein.

5 KU321639.1 Zika virus strain ZikaSPH2015, Brazil, complete genome (SEQ ID NO: 2)

GTTGTTACTGTTGCTGACTCAGACTGCGACAGTTCGAGTTTGAAGCGAAAGCTAGCAACAGTATCA
ACAGGTTTTATTTGGATTTGGAAACGAGAGTTTCTGGTCATGAAAAACCCAAAAAAGAAATCCGG
AGGATTCCGGATTGTCAATATGCTAAAACGCGGAGTAGCCCGTGTGAGCCCCTTTGGGGGCTTGAA
10 GAGGCTGCCAGCCGACTTCTGCTGGGTCATGGGCCCATCAGGATGGTCTTGCAATTCTAGCCTT
TTTGAGATTACAGGCAATCAAGCCATCACTGGGTCTCATCAATAGATGGGGTTTCAGTGGGGAAAA
AAGAGGCTATGGAATAATAAAGAAGTTCAAGAAAGATCTGGCTGCCATGCTGAGAATAATCAAT
GCTAGGAAGGAGAAGAAGAGACGGGGCGCAGATACTAGTGTGCGAATTGTTGGCCTCCTGCTGAC
CACAGCTATGGCAGCGGAGGTCCTAGACGTGGGAGTGCATACTATATGTACTTGGACAGAAACG
15 ATGCTGGGGAGGCCATATCTTTTCCAACCACATTGGGGATGAATAAGTGTTATATACAGATCATGG
ATCTTGGACACATGTGTGATGCCACCATGAGCTATGAATGCCCTATGCTGGATGAGGGGGTGGAA
CCAGATGACGTCGATTGTTGGTGCAACACGACGTCGAACCTTGGGTTGTGTACGGAACTGCCATCAC
AAAAAAGGTGAAGCACGGAGATCTAGAAGAGCTGTGACGCTCCCTCCCATTCACCTAGGAAGCT
GCAAACGCGGTGCGAAACCTGGTTGGAATCAAGAGAATACACAAAGCACTTGATTAGAGTCGAAA
ATTGGATATTCAGGAACCCTGGCTTCGCGTTAGCAGCAGCTGCCATCGCTTGGCTTTTGGGAAGCT
20 CAACGAGCCAAAAAGTCATATACTTGGTCATGATACTGCTGATTGCCCCGGCATAACAGCATCAGGT
GCATAGGAGTCAGCAATAGGGACTTTGTGGAAGGTATGTGAGGTGGGACTTGGGTTGATATTGTCT
TGGAACATGGAGGTTGTGTACCGTAATGGCACAGGACAAACCGACTGTGACATAGAGCTGGTT
ACAACAACAGTCAGCAACATGGCGGAGGTAAGATCCTACTGCTATGAGGCATCAATATCAGACAT
GGCTTCGGACAGCCGCTGCCCAACACAAGGTGAAGCCTACCTTGACAAGCAATCAGACACTCAAT
25 ATGTCTGCAAAAGAACGTTAGTGGACAGAGGCTGGGGAAATGGATGTGGACTTTTGGCAAAGGG
AGTCTGGTGACATGCGCTAAGTTTGCATGCTCCAAGAAAATGACCGGAAGAGCATCCAGCCAGA
GAATCTGGAGTACCGGATAATGTGTCAGTTTCATGGCTCCAGCACAGTGGGATGATCGTTAATGA
CACAGGACATGAAACTGATGAGAATAGAGCGAAGGTTGAGATAACGCCCAATTCACCAAGAGCC
GAAGCCACCCTGGGGGGTTTTGGAAAGCCTAGGACTTGATTGTGAACCGAGGACAGGCCTTGACTTT
30 TCAGATTTGTATTACTTGACTATGAATAACAAGCACTGGTTGGTTCACAAGGAGTGGTTCCACGAC
ATTCCATTACCTTGGCACGCTGGGGCAGACACCGGAACTCCACACTGGAACAACAAAGAAGCACT
GGTAGAGTTCAAGGACGCACATGCCAAAAGGCAAACTGTCTGGTTCTAGGGAGTCAAGAAGGAG
CAGTTCACACGGCCCTTGGCTGGAGCTCTGGAGGCTGAGATGGATGGTGCAAAAGGGAAGGCTGTCC
TCTGGCCACTTGAAATGTGCGCTGAAAATGGATAAACTTAGATTGAAGGGCGTGTCACTCCTTG
35 TGTACCGCAGCGTTCACATTCACCAAGATCCCGGCTGAAACACTGCACGGGACAGTCACAGTGA
GGTACAGTACGCAGGACAGATGGACCTTGAAGGTTCCAGCTCAGATGGCGGTGGACATGCAAA
CTCTGACCCCAAGTTGGGAGGTTGATAACCGCTAACCCCGTAATCACTGAAAGCACTGAGAACTCTA
AGATGATGCTGGAACCTTGATCCACCATTGTTGGGACTCTTACATTGTGATAGGAGTCGGGGAGAAG
AAGATCACCCACCACTGGCACAGGAGTGGCAGCACCATTGGAAAAGCATTGAAAGCCACTGTGAG
40 AGGTGCCAAGAGAATGGCAGTCTTGGGAGACACAGCCTGGGACTTTGGATCAGTTGGAGGCGCTC
TCAACTCATTGGGCAAGGGCATCCATCAAATTTTGGAGCAGCTTTCAAATCATTGTTTGGAGGAA
TGTCCTGGTTCTCACAAATTCTCATTGGAACGTTGCTGATGTGGTTGGGTCTGAACACAAAGAATG
GATCTATTTCCCTTATGTGCTTGGCCTTAGGGGGAGTGTTGATCTTCTTATCCACAGCCGCTCTGC
TGATGTGGGGTGCTCGGTGGACTTCTCAAAGAAGGAGACGAGATGCGGTACAGGGGTGTTCTGTCT
45 ATAACGACGTTGAAGCCTGGAGGGACAGGTACAAGTACCATCCTGACTCCCCCGTAGATTGGCA
GCAGCAGTCAAGCAAGCCTGGGAAGATGGTATCTGCGGGATCTCCTCTGTTTCAAGAATGGAAAA
CATCATGTGGAGATCAGTAGAAGGGGAGCTCAACGCAATCCTGGAAGAGAATGGAGTTCAACTGA
CGGTCGTTGTGGGATCTGTAAAAAACCCCATGTGGAGAGGTCCACAGAGATTGCCCGTGCCTGTG
AACGAGCTGCCCCACGGCTGGAAGGCTTGGGGGAAATCGCACTTCGTGAGAGCAGCAAAGACAAA
50 TAACAGCTTTGTCTGGATGGTGACACACTGAAGGAATGCCCACTCAAACATAGAGCATGGAACA
GCTTTCTTGTGGAGGATCATGGGTTCTGGGGTATTTACACTAGTGTCTGGCTCAAGGTTAGAGAAG
ATTATTCATTAGAGTGTGATCCAGCCGTTATTGGAACAGCTGTTAAGGGAAAGGAGGCTGTACACA
GTGATCTAGGCTACTGGATTGAGAGTGAGAAGAATGACACATGGAGGCTGAAGAGGGCCCATCTG

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KU497555.1 Zika virus isolate Brazil-ZKV2015, Brazil, complete genome (SEQ ID NO: 3)

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KU501215.1 Zika virus strain PRVABC59, Puerto Rico, complete genome (SEQ ID NO: 4)

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KU509998.1 Zika virus strain Haiti/1225/2014, Haiti, complete genome (SEQ ID NO: 5)

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KU527068.1 Zika virus strain Natal RGN, Brazil: Rio Grande do Norte, Natal, complete

55 genome (SEQ ID NO: 6)

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KU681081.3 Zika virus isolate Zika virus/H.sapiens-tc/THA/2014/SV0127- 14, Thailand,
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KU681082.3 Zika virus isolate Zika virus/H.sapiens-tc/PHL/2012/CPC-0740, Philippines,

55 complete genome (SEQ ID NO: 8)

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KU744693.1 Zika virus isolate VE_Ganxian, China, complete genome (SEQ ID NO: 10)

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LC002520.1 Zika virus genomic RNA, strain: MR766-NIID, Uganda, complete genome

50 (SEQ ID NO: 11)

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AY632535.2 NC_012532.1 Zika virus strain MR 766, Uganda, complete genome (SEQ ID

50 NO: 12)

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>Chimeric Asian ZIKV Sequence H/PF/2013 polyprotein flanked with consensus sequence

50 from other strains (SEQ ID NO: 13)

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AAGAGGCTATGGAAATAATAAAGAAGTTCAAGAAAGATCTGGCTGCCATGCTGAGAATAATCAAT
 GCTAGGAAGGAGAAGAAGAGACGAGGCGCAGATACTAGTGTGCGAATTGTTGGCCTCCTGCTGAC
 CACAGCTATGGCAGCGGAGGTCCTAGACGTGGGAGTGCATACTATATGTACTTGGACAGAAACG
 ACGCTGGGGAGGCCATATCTTTTCCAACCACATTGGGGATGAATAAGTGTTATATACAGATCATGG
 5 ATCTTGGACACATGTGTGATGCCACCATGAGCTATGAATGCCCTATGCTGGATGAGGGGGTGGAA
 CCAGATGACGTCCGATTGTTGGTGCAACACGACGTCAACTTGGGTTGTGTACGGAACCTGCCATCAC
 AAAAAAGGTGAAGCACGGAGATCTAGAAGAGCTGTGACGCTCCCCCTCCCATTTCCACTAGGAAGCT
 GCAAACGCGGTTCGCAAACCTGGTTGGAATCAAGAGAATACACAAAGCACTTGATTAGAGTCGAAA
 ATTGGATATTAGGAACCCCTGGCTTCGCGTTAGCAGCAGCTGCCATCGCTTGGCTTTTGGGAAGCT
 10 CAACGAGCCAAAAGTCATATACTTGGTCATGATACTGCTGATTGCCCCGGCATACAGCATCAGGT
 GCATAGGAGTCAGCAATAGGGACTTTGTGGAAGGTATGTCAGGTGGGACTTGGGTTGATGTTGTCT
 TGGAACATGGAGGTTGTGTACCGTAATGGCACAGGACAAACCGACTGTCGACATAGAGCTGGTT
 ACAACAACAGTCAGCAACATGGCGGAGGTAAGATCCTACTGCTATGAGGCATCAATATCGGACAT
 GGCTTCGGACAGCCGCTGCCCAACACAAGGTGAAGCCTACCTTGACAAGCAATCAGACACTCAAT
 15 ATGTCTGCAAAAGAACGTTAGTGGACAGAGGCTGGGGAAATGGATGTGGACTTTTGGCAAAGGG
 AGCCTGGTGACATGCGCTAAGTTGTCATGCTCCAAGAAAATGACCGGGAAGAGCATCCAGCCAGA
 GAATCTGGAGTACCGGATAATGCTGTCAGTTTCATGGCTCCAGCACAGTGGGATGATCGTTAATGA
 CACAGGACATGAACTGATGAGAATAGAGCGAAGGTTGAGATAACGCCCAATTCACCAAGAGCC
 GAAGCCACCCTGGGGGGTTTGGAAAGCCTAGGACTTGATTGTGAACCGAGGACAGGCCCTTGACTTT
 20 TCAGATTGTATTACTTGACTATGAATAACAAGCACTGGTTGGTTCACAAGGAGTGGTTCCACGAC
 ATTCCATTACCTTGGCACGCTGGGGCAGACACCGGAACTCCACACTGGAACAACAAGAAGCACT
 GGTAGAGTTCAAGGACGCACATGCCAAAAGGCAAACTGTCTGGTTCTAGGGAGTCAAGAAGGAG
 CAGTTCACACGGCCCTTGCTGGAGCTCTGGAGGCTGAGATGGATGGTGCAAAGGGAAGGCTGTCC
 TCTGGCCACTTGAAATGTCGCCTGAAAATGGATAAACTTAGATTGAAGGGCGTGTCTACTCCTTG
 25 TGTACCGCAGCGTTCACATTCACCAAGATCCCGGCTGAAACACTGCACGGGACAGTCACAGTGG
 GGTACAGTACGCAGGGACAGATGGACCTTGCAAGGTTCCAGCTCAGATGGCGGTGGACATGCAAA
 CTCTGACCCCAAGTTGGGAGGTTGATAACCGCTAACCCCGTAATCACTGAAAGCACTGAGAACTCTA
 AGATGATGCTGGAACCTTGATCCACCATTTGGGGACTCTTACATTGTTCATAGGAGTCGGGGAGAAG
 AAGATCACCCACCCTGGCACAGGAGTGGCAGCACCATTGGAAAAGCATTGGAAGCCACTGTGAG
 30 AAGTGCCAAAGAAATGGCAGTCTTGGGAGACACAGCTGGGACTTTGGATCAGTTGGAGGCGCTC
 TCAATCAATTGGGCAAGGGCATCCATCAAATTTTGGAGCAGCTTTCAAATCATTTGTTGGAGGAA
 TGTCTTGGTTCTCACAAATTTCTCATTGGAACGTTGCTGATGTGGTTGGGTCTGAACACAAAGAATG
 GATCTATTTCCCTTATGTGCTTGGCCTTAGGGGGAGTGTTGATCTTCTTATCCACAGCTGTCTCTGC
 TGATGTGGGGTGCTCGGTGGACTTCTCAAAGAAGGAGACGAGATGCGGTACAGGGGTGTTCTGTCT
 35 ATAACGACGTTGAAGCCTGGAGGGACAGGTACAAGTACCATCCTGACTCCCCCGTAGATTGGCA
 GCAGCAGTCAAGCAAGCCTGGGAAGATGGTATCTGTGGGATCTCCTCTGTTTCAAGAATGAAAA
 CATCATGTGGAGATCAGTAGAAGGGGAGCTCAACGCAATCCTGGAAGAGAATGGAGTTCAACTGA
 CGGTCGTTGTGGGATCTGTAAAAAACCCCATGTGGAGAGGTCCACAGAGATTGCCCCGTGCCTGTG
 AACGAGCTGCCCCACGGCTGGAAGGCTTGGGGGAAATCGTACTTCGTACAGAGCAGCAAAGACAAA
 40 TAACAGCTTTGTGCTGGATGGTGACACACTGAAGGAATGCCCACTCAAACATAGAGCATGGAACA
 GCTTTCTTGTGGAGGATCATGGGTTGCGGGTATTTGACACTAGTGTCTGGCTCAAGGTTAGAGAAG
 ATTATTCAATTAGAGTGTGATCCAGCCGTTATTGGAACAGCTGTTAAGGGAAAGGAGGCTGTACACA
 GTGATCTAGGCTACTGGATTGAGAGTGAGAAGAATGACACATGGAGGCTGAAGAGGGCCCATCTG
 ATCGAGATGAAAACATGTGAATGGCCAAAGTCCCACACATTGTGGACAGATGGAATAGAAGAGA
 45 GTGATCTGATCATACCCAAGTCTTTAGCTGGGCCACTCAGCCATCACAATACCAGAGAGGGCTACA
 GGACCCAAATGAAAGGGCCATGGCACAGTGAAGAGCTTGAAATTCGGTTTGAGGAATGCCAGGC
 ACTAAGGTCCACGTGGAGGAAACATGTGGAACAAGAGGACCATCTCTGAGATCAACCACTGCAAG
 CGGAAGGGTGATCGAGGAATGGTGCTGCAGGGAGTGCACAAATGCCCCCACTGTCGTTCCGGGCTA
 AAGATGGCTGTTGGTATGGAATGGAGATAAGGCCCAGGAAAGAACCAGAAAGTAACTTAGTAAG
 50 GTCAATGGTGACTGCAGGATCAACTGATCAGATGGATCACTTCTCCCTTGGAGTGCTTGTGATCT
 GCTCATGGTGACGAAGGGCTGAAGAAGAGAATGACCACAAAGATCATCAAGACATCATGATG
 GCAGTGCTGGTAGCTATGATCCTGGGAGGATTTTCAATGAGTGACCTGGCTAAGCTTGCAATTTTG
 ATGGGTGCCACCTTCGCGGAAATGAACACTGGAGGAGATGTAGCTCATCTGGCGCTGATAGCGGC
 ATTCAAAGTCAGACCAGCGTTGCTGGTATCTTTTCATCTTCAGAGCTAATTGGACACCCCGTGAAAG
 55 CATGCTGCTGGCCTTGGCCTCGTGTCTTTTGCAAACCTGCGATCTCCGCTTGGAAAGGCGACCTGAT
 GGTCTCATCAATGGTTTTGCTTGGCCTGGTTGGCAATACGAGCGATGGTTGTTCCACGCACTGAT
 AACATCACCTTGGCAATCCTGGCTGCTCTGACACCACTGGCCCGGGGCACACTGCTTGTGGCGTGG

AGAGCAGGCCTTGCTACTTGCGGGGGGTTTATGCTCCTCTCTCTGAAGGGAAAAGGCAGTGTGAA
 GAAGAACTTACCATTTGTCATGGCCCTGGGACTAACCCTGTGAGGCTGGTCGACCCCATCAACGT
 GGTGGGACTGCTGTTGCTCACAAGGAGTGGGAAGCGGAGCTGGCCCCCTAGCGAAGTACTCACAG
 CTGTTGGCCTGATATGCGCATTGGCTGGAGGGTTCGCCAAGGCAGATATAGAGATGGCTGGGCCC
 5 ATGGCCGCGGTCTGGTCTGCTAATTGTCAGTTACGTGGTCTCAGGAAAGAGTGTGGACATGTACATT
 GAAAGAGCAGGTGACATCACATGGGAAAAAGATGCGGAAGTCACTGGAAACAGTCCCCGGCTCG
 ATGTGGCGCTAGATGAGAGTGGTGATTTCTCCCTGGTGGAGGATGACGGTCCCCCATGAGAGAG
 ATCATACTCAAGGTGGTCCTGATGACCATCTGTGGCATGAACCCAATAGCCATACCCTTTGCAGCT
 GGAGCGTGGTACGTATACGTGAAGACTGGAAAAAGGAGTGGTGCTCTATGGGATGTGCCTGCTCC
 10 CAAGGAAGTAAAAAGGGGGGAGACCACAGATGGAGTGTACAGAGTAATGACTCGTAGACTGCTA
 GGTTCAACACAAGTTGGAGTGGGAGTTATGCAAGAGGGGGTCTTTCACACTATGTGGCACGTAC
 AAAAGGATCCGCGCTGAGAAGCGGTGAAGGGAGACTTGATCCATACTGGGGAGATGTCAAGCAG
 GATCTGGTGTACATACTGTGGTCCATGGAAGCTAGATGCCGCTGGGACGGGCACAGCGAGGTGCA
 GCTCTTGGCCGTGCCCCCGGAGAGAGAGCGAGGAACATCCAGACTCTGCCCCGAATATTTAAGA
 15 CAAAGGATGGGGACATTGGAGCGGTTGCGCTGGATTACCCAGCAGGAACCTTCAGGATCTCCAATC
 CTAGACAAGTGTGGGAGAGTGATAGGACTTTATGGCAATGGGGTCGTGATCAAAAATGGGAGTTA
 TGTTAGTGCCATCACCCAAGGGAGGAGGGAGGAAGAGACTCCTGTTGAGTGTCTCGAGCCTTCGA
 TGCTGAAGAAGAAGCAGCTAACTGTCTTAGACTTGCATCCTGGAGCTGGGAAAACCAGGAGAGTT
 CTTCTGAAATAGTCCGTGAAGCCATAAAAAAGACTCCGTAAGTGTGATCTTAGCTCCAACAGG
 20 GTTGCTCGTCTGAAATGGAGGAAGCCCTTAGAGGGCTTCCAGTGCCTATATGACAACAGCAGTC
 AATGTCAACCCACTCTGGAACAGAAATCGTCACTTAATGTGCCATGCCACCTTCACTTCACTGCTA
 CTACAGCCAATCAGAGTCCCCAACTATAATCTGTATATTATGGATGAGGCCCCACTTCACAGATCCC
 TCAAGTATAGCAGCAAGAGGATACATTTCAACAAGGGTTGAGATGGGCGAGGCGGCTGCCATCTT
 CATGACCGCCACGCCACCAGGAACCCGTGACGCATTTCCGGACTCCAACCTACCAATTATGGACAC
 25 CGAAGTGGAAAGTCCCAGAGAGAGCCTGGAGCTCAGGCTTTGATTGGGTGACGGATCATTCTGGAA
 AAACAGTTTGGTTTGTTCGAAGCGTGAGGAACGCCAATGAGATCGCAGCTTGTCTGACAAAAGGCT
 GGAAAACGGGTCATACAGCTCAGCAGAAAGACTTTTGAGACAGAGTTCCAGAAAAACAAAACATCA
 AGAGTGGGACTTTGTCTGACAACCTGACATTTAGAGATGGGCGCCAACCTTTAAAGCTGACCGTGT
 CATAGATTCCAGGAGATGCCTAAAGCCGGTCACTTGTATGGCGAGAGAGTCACTTCTGGCTGGAC
 30 CCATGCCTGTGACACATGCCAGCGTGGCCAGAGGAGGGGGCGCATAGGCAGGAATCCCAACAAA
 CCTGGAGATGAGTATCTGTATGGAGGTGGGTGCGCAGAGACTGACGAAGACCATGCACATGGCT
 TGAAGCAAGAATGCTCCTTGACAATATTTACCTCCAAGATGGCCTCATAGCCTCGCTCTATCGACC
 TGAGGCCGACAAAAGTAGCAGCCATTGAGGGAGAGTTCAAGCTTAGGACGGAGCAAAGGAAGACC
 TTTGTGGAACCTCATGAAAAGAGGAGATCTTCCTGTTTGGCTGGCCTATCAGGTTGCATCTGCCGGA
 35 ATAACCTACACAGATAGAAGATGGTGCTTTGATGGCAGCACCAACAACACCATAATGGAAGACAG
 TGTGCCGGCAGAGGTGTGGACCAGACACGGAGAGAAAAAGAGTGTCAAACCGAGGTGGATGGAC
 GCCAGAGTTTGTTCAGATCATGCGGCCCTGAAGTCATTCAAGGAGTTTGCCGCTGGGAAAAGAGG
 AGCGGCTTTTGGAGTGATGGAAGCCCTGGGAACACTGCCAGGACACATGACAGAGAGATTCCAGG
 AAGCCATTGACAACCTCGCTGTGCTCATGCGGGCAGAGACTGGAAGCAGGCCTTACAAAGCCGCG
 40 GCGGCCCAATTGCCGGAGACCCTAGAGACCATATGCTTTTGGGGTGTGGGAACAGTCTCGCTG
 GGAATCTTTTTCGTCTTGATGAGGAACAAGGCTATAGGGAAGATGGGCTTTGGAATGGTGACTCTT
 GGGGCCAGCGCATGGCTCATGTGGCTCTCGGAAATTGAGCCAGCCAGAATTGCATGTGTCTCTATT
 GTTGTGTTCTATTGCTGGTGGTGCTCATACCTGAGCCAGAAAAAGCAAAGATCTCCCCAGGACAAC
 CAAATGGCAATCATCATCATGGTAGCAGTAGGTCTTCTGGGCTTGATTACCGCCAATGAACTCGGA
 45 TGGTTGGAGAGAAACAAAGAGTGACCTAAGCCATCTAATGGGAAGGAGAGAGGAGGGGGCAACCA
 TAGGATTCTCAATGGACATTGACCTGCGGCCAGCCTCAGCTTGGGCCATCTATGCTGCCTTGACAA
 CTTTCATTACCCCAGCCGTCCAACATGCAGTGACCACTTCATACAACAACCTACTCCTTAATGGCGA
 TGGCCACGCAAGCTGGAGTGTTGTTTGGTATGGGCAAAGGGATGCCATTCTACGCATGGGACTTTG
 GAGTCCCCTGCTAATGATAGGTTGCTACTCACAATTAACACCCCTGACCCTAATAGTGGCCATCA
 50 TTTTGTCTGTGGCGCACTACATGTACTTGATCCCAGGGCTGCAGGCAGCAGCTGCGCGTGTGCCC
 AGAAGAGAACGGCAGCTGGCATCATGAAGAACCCTGTTGTGGATGGAATAGTGGTGACTGACATT
 GACACAATGACAATTGACCCCCAAGTGGAGAAAAAGATGGGACAGGTGCTACTCATAGCAGTAGC
 CGTCTCCAGCGCCATACTGTGCGGGACCGCCTGGGGGTGGGGGGAGGCTGGGGCCCTGATCACAG
 CGGCAACTTCCACTTTGTGGGAAGGCTCTCCGAACAAGTACTGGAACCTCTACAGCCACTTCAC
 55 TGTGTAACATTTTATAGGGGAAGTTACTTGGCTGGAGCTTCTCTAATCTACACAGTAACAAGAAACG
 CTGGCTTGGTCAAGAGACGTGGGGGTGGAACAGGAGAGACCCTGGGAGAGAAATGGAAGGCCCG
 CTTGAACCAGATGTCGGCCCTGGAGTTCTACTCCTACAAAAAGTCAGGCATCACCGAGGTGTGCAG

AGAAGAGCCCCGCCGCGCCCTCAAGGACGGTGTGGCAACGGGAGGCCATGCTGTGTCCGAGGAA
 GTGCAAAGCTGAGATGGTTGGTGGAGCGGGGATACCTGCAGCCCTATGGAAAGGTCATTGATCTT
 GGATGTGGCAGAGGGGGCTGGAGTTACTACGCCGCCACCATCCGCAAAGTTCAAGAAGTGAAAGG
 ATACACAAAAGGAGGCCCTGGTCATGAAGAACCCATGTTGGTGCAAAGCTATGGGTGGAACATAG
 5 TCCGTCTTAAGAGTGGGGTGGACGTCTTTCATATGGCGGCTGAGCCGTGTGACACGTTGCTGTGTG
 ACATAGGTGAGTCATCATCTAGTCCTGAAGTGGAAGAAGCACGGACGCTCAGAGTCCTCTCCATG
 GTGGGGGATTGGCTTGAAAAAAGACCAGGAGCCTTTTGTATAAAAAGTGTTGTGCCCATACACCAG
 CACTATGATGGAAACCTTGGAGCGACTGCAGCGTAGGTATGGGGGAGGACTGGTCAGAGTGCCAC
 TCTCCCGCAACTCTACACATGAGATGTACTGGGTCTCTGGAGCGAAAAGCAACACCATAAAAAGT
 10 GTGTCCACCACGAGCCAGCTCCTCTTGGGGCGCATGGACGGGCCAGGAGGCCAGTGAAATATGA
 GGAGGATGTGAATCTCGGCTCTGGCACGCGGGCTGTGGTAAGCTGCGCTGAAGCTCCCAACATGA
 AGATCATTTGGTAACCGCATTGAAAGGATCCGCAGTGAGCACGCGGAAACGTGGTTCTTTGACGAG
 AACCACCCATATAGGACATGGGCTTACCATGGAAGCTATGAGGCCCCACACAAGGGTCAGCGTC
 CTCTCTAATAAACGGGGTTGTGAGGCTCCTGTCAAAACCCTGGGATGTGGTGACTGGAGTCACAGG
 15 AATAGCCATGACCGACACCACACCGTATGGTCAGCAAAGAGTTTTCAAGGAAAAAGTGGACACTA
 GGGTGCCAGACCCCAAGAAGGCACCTCGTCAGGTTATGAGCATGGTCTCTTCCCTGGTTGTGGAAAG
 AGCTAGGCAAAACACAAACGGGCCACGAGTCTGTACCAAGAAGAGTTTCATCAACAAGGTTTCGTAGC
 AATGCAGCATTAGGGGCAATATTTGAAGAGGAAAAAGAGTGGAAGACTGCAGTGGAAGCTGTGA
 ACGATCCAAGGTTCTGGGCTCTAGTGGACAAGGAAAGAGAGCACCACCTGAGAGGAGAGTGCCA
 20 GAGTTGTGTGTACAACATGATGGGAAAAAGAGAAAAAGAAACAAGGGGAATTTGGAAAGGCCAAG
 GGCAGCCGCGCCATCTGGTATATGTGGCTAGGGGCTAGATTTCTAGAGTTTGAAGCCTTGGATTCT
 TTGAACGAGGATCACTGGATGGGGAGAGAGAACTCAGGAGGTGGTGTGTAAGGGCTGGGATTACA
 AAGACTCGGATATGTCCTAGAAGAGATGAGTCGCATACCAGGAGGAAGGATGTATGCAGATGACA
 CTGCTGGCTGGGACACCCGCATCAGCAGGTTTGTATCTGGAGAATGAAGCTCTAATCACCAACCAA
 25 ATGGAGAAAGGGCACAGGGCCTTGGCATTGGCCATAATCAAGTACACATACCAAAACAAAGTGGT
 AAAGGTCCTTAGACCAGCTGAAAAAGGGAAAGACAGTTATGGACATTATTTGAGACAAGACCAAA
 GGGGGAGCGGACAAGTTGTCACCTTACGCTCTTAACACATTTACCAACCTAGTGGTGCAACTCATTC
 GGAATATGGAGGCTGAGGAAGTTCTAGAGATGCAAGACTTGTGGCTGCTGCGGAGGTGAGAGAAA
 GTGACCAACTGGTTGCAGAGCAACGGATGGGATAGGCTCAAACGAATGGCAGTCAGTGAGATGA
 30 TTGCGTTGTGAAGCCAATTGATGATAGGTTTGCACATGCCCTCAGGTTCTTGAATGATATGGGAAA
 AGTTAGGAAGGACACACAAGAGTGGAACCCCTCAACTGGATGGGACAACCTGGGAAGAAGTTCCG
 TTTTGCTCCCACTTCAACAAGCTCCATCTCAAGGACGGGAGGTCCATTGTGGTTCCCTGCCGC
 CACCAAGATGAACTGATTGGCCGGGCGCGCTCTCTCCAGGGGCGGGATGGAGCATCCGGGAGAC
 TGCTTGCTAGCAAAATCATATGCGCAAATGTGGCAGCTCCTTTATTTCCACAGAAGGGACCTCCG
 35 ACTGATGGCCAATGCCATTTGTTTCATCTGTGCCAGTTGACTGGGTCCAAGTGGGAGAACTACCTG
 GTCAATCCATGGAAAGGGAGAATGGATGACCACTGAAGACATGCTTGTGGTGTGGAACAGAGTGT
 GGATTGAGGAGAACGACCACATGGAAGACAAGACCCAGTTACGAAATGGACAGACATTCCCTAT
 TTGGGAAAAAGGGAAGACTTGTGGTGTGGATCTCTCATAGGGCACAGACCGCGCACCACTGGGC
 TGAGAACATTAACACAGTCAACATGGTGGCAGGATCATAGGTGATGAAGAAAAGTACATGG
 40 ACTACCTATCCACCAAGTTCGCTACTTGGGTGAAGAAGGGTCTACACCTGGAGTGCTGTAAGCAC
 CAATCTTAGTGTTGTGTCAGGCCTGCTAGTCAGCCACAGCTTGGGGAAAGCTGTGCAGCCTGTGACCC
 CCCCAGGAGAAGCTGGGAAACCAAGCCTATAGTCAGGCCGAGAACGCCATGGCACGGAAGAAGC
 CATGCTGCCTGTGAGCCCCCTCAGAGGACACTGAGTCAAAAAACCCACGCGCTTGGAGGCGCAGG
 ATGGGAAAAAGAGGTGGCGACCTTCCCCACCTTCAATCTGGGGCCTGAACTGGAGATCAGCTGT
 45 GGATCTCCAGAAGAGGGACTAGTGGTTAGAGGAGACCCCCCGAAAACGCAAAACAGCATATTG
 ACGCTGGGAAAGACCAGAGACTCCATGAGTTCCACCACGCTGGCCGCCAGGCACAGATCGCCGA
 ATAGCGGCGCGCGGTGTGGGGAAATCC

50 In some embodiments, the Zika virus has a RNA genome corresponding to the DNA
 sequence provided by the nucleic acid sequence of any one of SEQ ID NOs: 2-13. In some
 embodiments, the Zika virus has a variant genome that is at least 80%, 81%, 82%, 83%, 84%,

PAT018/EP/PR1

85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%,
99.5%, 99.6%, 99.7%, 99.8% or 99.9% identical to any one of SEQ ID NOs: 2-13.

Provided below are amino acid sequences of the E-proteins of Zika strains that may
5 be used in the methods, compositions, and/or vaccines described herein.

isol-ARB15076.AHF49784.1.Central_African_Republic/291-788 Flavivirus envelope glycoprotein E. (SEQ ID NO: 14)

10 IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
LEYRIMLSVHGSQHSGMIVNDENRAKVEVTPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLYYLTMMN
KHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTALAGAL
EAEMDGAKGRLFSGHLKCRLLKMDKRLRLKGVSYSLCTAAFTFTKVPÄETLHGTVTVEVQYAGTDGPCK
15 VPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHRSGSTIGK
AFEATVRGAKRMAVLGDTAWDFGSVGGVFNSLKGKGIHQIFGAAFKSLFGGMSWFSQILIGTLLVWLGL
NTKNGSISLTCLALGGVMIFLSTAVSA

isol-IbH_30656.AEN75265.1.Nigeria/291-788 Flavivirus envelope glycoprotein E. (SEQ ID NO: 15)

20 IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
LEYRIMLSVHGSQHSGMIVNDENRAKVEVTPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLYYLTMMN
KHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTALAGAL
EAEMDGAKGRLSSGHLKCRLLKMDKRLRLKGVSYSLCTAAFTFTKVPÄETLHGTVTVEVQYAGRDGPCK
25 VPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHRSGSIIGK
AFEATVRGAKRMAVLGDTAWDFGSVGGVFNSLKGKGIHQIFGAAFKSLFGGMSWFSQILIGTLLVWLGL
NTKNGSISLTCLALGGVMIFLSTAVSA

ArB1362.AHL43500.1.-/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 16)

30 IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
LEYRIMLSVHGSQHSGMIVNDXXXXXXXNRAEVEVTPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YLTMMNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
ALAGALEAEMDGAKGRLFSGHLKCRLLKMDKRLRLKGVSYSLCTAAFTFTKVPÄETLHGTVTVEVQYA
35 GTDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWH
RSGSTIGKA FEATVRGAKRMAVLGDTAWDFGSVGGVFNSLKGKGIHQIFGAAFKSLFGGMSWFSQILIG
TLLVWLGLNTKNGSISLTCLALGGVMIFLSTAVSA

ArD128000.AHL43502.1.-/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 17)

40 IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
LEYRIMLSVHGSQHSGMXXXXXGHETDENRAKVEVTPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YLTMMNKHRLVRKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
ALAGALEAEMDGAKGRLFSGHLKCRLLKMDKRLRLKGVSYSLCTAAFTFTKVPÄETLHGTVTVEVQYA
45 GTDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWL
KKGSSIGKA FEATVRGAKRMAVLGDTAWDFGSVGGVFNSLKGKVHQIFGAAFKSLFGGMSWFSQILIG
TLLVWLGLNTKNGSISLTCLALGGVMIFLSTAVSA

ArD158095.AHL43505.1.-/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 18)

50 IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
LEYRIMLSVHGSQHSGMIVNDIGHETDENRAKVEVTPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLYY
LTMNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTA
LAGALEAEMDGAKGRLFSGHLKCRLLKMDKRLRLKGVSYSLCTAAFTFTKVPÄETLHGTVTVEVQYAGT
DGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHR

GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGVFNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
LVWLGLNTKNGSISLTCLALGGVMIFLSTAVSA

ArD158084.AHL43504.1.-/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 19)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTFSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
LEYRIMLSVHGSQHSGMIVNDIGHETDENRAKVEVTPNSPRAEATLGGFGLSLDCEPRTGLDFSDLYY
LTMNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTA
LAGALEAEMDGAAGRLFSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKVPAETLHGTVTVEVQYAGT
DGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHR
GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGVFNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
LVWLGLNTKNGSISLTCLALGGVMIFLSTAVSA

isol-ARB13565.AHF49783.1.Central_African_Republic/291-794 Flavivirus envelope glycoprotein
E. (SEQ ID NO: 20)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTFSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
LEYRIMLSVHGSQHSGMIVNDIGHETDENRAKVEVTPNSPRAEATLGGFGLSLDCEPRTGLDFSDLYY
LTMNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTA
LAGALEAEMDGAAGRLFSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKVPAETLHGTVTVEVQYAGT
DGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHR
GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGVFNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
LVWLGLNTKNGSISLTCLALGGVMIFLSTAVSA

isol-ARB7701.AHF49785.1.Central_African_Republic/291-794 Flavivirus envelope glycoprotein
E. (SEQ ID NO: 21)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTFSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
LEYRIMLSVHGSQHSGMIVNDIGHETDENRAKVEVTPNSPRAEATLGGFGLSLDCEPRTGLDFSDLYY
LTMNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTA
LAGALEAEMDGAAGRLFSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKVPAETLHGTVTVEVQYAGT
DGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHR
GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGVFNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
LVWLGLNTKNGSISLTCLALGGVMIFLSTAVSA

isol-ArD_41519.AEN75266.1.Senegal/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO:
22)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTFSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
LEYRIMLSVHGSQHSGMIVNDIGHETDENRAKVEVTPNSPRAEATLGGFGLSLDCEPRTGLDFSDLY
YLTMMNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
ALAGALEAEMDGAAGRLFSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKVPAETLHGTVTVEVQYA
GTDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHR
RSGSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGVFNSLKGKIHQIFGAAFKSLFGGMSWFSQILIG
TLLVWLGLNTKNGSISLTCLALGGVMIFLSTAVSA

MR766-NIID.BAP47441.1.Uganda/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO:
23)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTFSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
LEYRIMLSVHGSQHSGMTVNDIGYETDENRAKVEVTPNSPRAEATLGGFGLSLDCEPRTGLDFSDLY
YLTMMNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
ALAGALEAEMDGAAGKLFSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKVPAETLHGTVTVEVQYA
GTDGPCKIPVQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHR
SGSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGVFNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
LVWLGLNTKNGSISLTCLALGGVMIFLSTAVSA

LC002520.1/326-829 Zika virus genomic RNA, strain: MR766-NIID, Uganda, Flavivirus
envelope glycoprotein E. (SEQ ID NO: 24)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
 LEYRIMLSVHGSQHSGMTVNDIGYETDENRAKVEVTPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 5 ALAGALEAEMDGAAGKGLFSGHLKCRKMDKRLRLKGVSYSLCTAAFTFTKVPAETLHGTVTVEVQYA
 GTDGPCKIPVQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHR
 SGSTIGKAFEATVRGAKRMAVLGDTAWDFGSGGVFNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
 LVWLGLNTKNGSISLTCLALGGVMIFLSTAVSA

isol-MR_766.AEN75263.1.Uganda/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 25)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
 LEYRIMLSVHGSQHSGMIVNDIGYETDENRAKVEVTPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 10 ALAGALEAEMDGAAGKGLFSGHLKCRKMDKRLRLKGVSYSLCTAAFTFTKVPAETLHGTVTVEVQYA
 GTDGPCKIPVQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHR
 15 SGSTIGKAFEATVRGAKRMAVLGDTAWDFGSGGVFNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
 LVWLGLNTKNGSISLTCLALGGVMIFLSTAVSA

ArD7117.AHL43501.1.-/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 26)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
 LEYRIMLSVHGSQHSGMIVNDIGHETDENRAKVEVTPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 LTMNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTA
 20 LAGALEAEMDGAAGRLFSGHLKCRKMDKRLRLKGVSYSLCTAVCTAAKVPAETLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHR
 25 SGSTIGKAFEATVRGAKRMAVLGDTAWDFGSGGVFNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
 LVWLGLNTKNGSISLTCLALGGVMIFLSTAVSA

AY632535.2/326-825 NC_012532.1 Zika virus strain MR 766, Uganda, Flavivirus envelope glycoprotein E. (SEQ ID NO: 27)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
 LEYRIMLSVHGSQHSGMIGYETDEDRAKVEVTPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLYYLT
 30 NNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTALAG
 ALEAEMDGAAGRLFSGHLKCRKMDKRLRLKGVSYSLCTAAFTFTKVPAETLHGTVTVEVQYAGTDGP
 CKIPVQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHRSGSTI
 35 GKAFEATVRGAKRMAVLGDTAWDFGSGGVFNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTLVW
 LGLNTKNGSISLTCLALGGVMIFLSTAVSA

MR_766.AAV34151.1.Uganda/291-790 Flavivirus envelope glycoprotein E.

IQ32ZE1IQ32ZE1_9FL (SEQ ID NO: 28)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
 LEYRIMLSVHGSQHSGMIGYETDEDRAKVEVTPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLYYLT
 40 NNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTALAG
 ALEAEMDGAAGRLFSGHLKCRKMDKRLRLKGVSYSLCTAAFTFTKVPAETLHGTVTVEVQYAGTDGP
 CKIPVQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHRSGSTI
 45 GKAFEATVRGAKRMAVLGDTAWDFGSGGVFNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTLVW
 LGLNTKNGSISLTCLALGGVMIFLSTAVSA

MR_766.YP_009227198.1.Uganda/1-500 envelope protein E [Zika virus] (SEQ ID NO: 29)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
 LEYRIMLSVHGSQHSGMIGYETDEDRAKVEVTPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLYYLT
 50 NNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTALAG
 ALEAEMDGAAGRLFSGHLKCRKMDKRLRLKGVSYSLCTAAFTFTKVPAETLHGTVTVEVQYAGTDGP
 CKIPVQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHRSGSTI
 GKAFEATVRGAKRMAVLGDTAWDFGSGGVFNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTLVW
 55 LGLNTKNGSISLTCLALGGVMIFLSTAVSA

KU681081.3/308-811 Zika virus isolate Zika virus/H.sapiens-tc/THA/2014/SV0127- 14, Thailand, Flavivirus envelope glycoprotein E. (SEQ ID NO: 30)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHWLVHKEWFHDIPLPWHTGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 ALAGALEAEMDGAAGRLSSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITEGTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHR
 SGSTIGKAFAEATVRGAKRMAVLGDTAWDFGSVGGVLSLKGKIHQIFGAAFKSLFGGMSWFSQILIGT
 LLMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

isol-Zika_virus%*H.sapiens-tc*%THA%2014%SV0127-_14.AMD61710.1.Thailand/291-794
 Flavivirus envelope glycoprotein E. (SEQ ID NO: 31)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHWLVHKEWFHDIPLPWHTGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 ALAGALEAEMDGAAGRLSSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITEGTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHR
 SGSTIGKAFAEATVRGAKRMAVLGDTAWDFGSVGGVLSLKGKIHQIFGAAFKSLFGGMSWFSQILIGT
 LLMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

CK-ISL_2014.AIC06934.1.Cook_Islands/1-504 Flavivirus envelope glycoprotein E. (Fragment)
 OS=Zika virus GN=E PE=4 SV=1 (SEQ ID NO: 32)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHWLVHKEWFHDIPLPWHTGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 ALAGALEAEMDGAAGRLSSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITEGTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHR
 GSTIGKAFAEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGT
 LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

Natal_RGN.AMB18850.1.Brazil:_Rio_Grande_do_Norte,_Natal/291-794 Flavivirus envelope
 glycoprotein E.] (SEQ ID NO: 33)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHWLVHKEWFHDIPLPWHTGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 ALAGALEAEMDGAAGRLSSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITEGTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHR
 GSTIGKAFAEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGT
 LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

isol-Si323.AMC37200.1.Colombia/1-504 Flavivirus envelope glycoprotein E. (SEQ ID NO: 34)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHWLVHKEWFHDIPLPWHTGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 ALAGALEAEMDGAAGRLSSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITEGTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHR
 GSTIGKAFAEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGT
 LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

KU707826.1/317-820 Zika virus isolate SSABR1, Brazil, Flavivirus envelope glycoprotein E.
 (SEQ ID NO: 35)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHWLVHKEWFHDIPLPWHTGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT

ALAGALEAEMDGAAGRLSSGHLKCRLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
GSTIGKAFAEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

5 KU509998.1/326-829 Zika virus strain Haiti/1225/2014, Haiti, Flavivirus envelope glycoprotein E. (SEQ ID NO: 36)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDTGHTDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
10 YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
ALAGALEAEMDGAAGRLSSGHLKCRLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
GSTIGKAFAEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

15 isol-GDZ16001.AML82110.1.China/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 37)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDTGHTDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
20 YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
ALAGALEAEMDGAAGRLSSGHLKCRLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
GSTIGKAFAEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

25 BeH819015.AMA12085.1.Brazil/291-794 Flavivirus envelope glycoprotein E.] (SEQ ID NO: 38)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDTGHTDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
30 ALAGALEAEMDGAAGRLSSGHLKCRLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
GSTIGKAFAEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

35 MRS_OPY_Martinique_PaRi_2015.AMC33116.1.Martinique/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 39)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDTGHTDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
40 ALAGALEAEMDGAAGRLSSGHLKCRLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
GSTIGKAFAEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

45 KU501215.1/308-811 Zika virus strain PRVABC59, Puerto Rico, Flavivirus envelope glycoprotein E. (SEQ ID NO: 40)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDTGHTDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
50 ALAGALEAEMDGAAGRLSSGHLKCRLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
GSTIGKAFAEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

55 Haiti%1225%2014.AMB37295.1.Haiti/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 41)

IRCIGVSNRDFVEGMSGGTWVDVVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHEHETDENRAKVEITPNSPRAEATLGGFGLDCEPRTGLDFSDLY
 YLTMNNKHHLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 5 ALAGALEAEMDGAAGRLSSGHLKCRKMDKLRRLKGVSYSLCTAAFTFTKIPAEHLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
 LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

KU527068.1/308-811 Zika virus strain Natal RGN, Brazil: Rio Grande do Norte, Natal,

Flavivirus envelope glycoprotein E. (SEQ ID NO: 42)

IRCIGVSNRDFVEGMSGGTWVDVVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHEHETDENRAKVEITPNSPRAEATLGGFGLDCEPRTGLDFSDLY
 YLTMNNKHHLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 15 ALAGALEAEMDGAAGRLSSGHLKCRKMDKLRRLKGVSYSLCTAAFTFTKIPAEHLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
 LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

isol-Z1106027.ALX35662.1.Suriname/5-508 Flavivirus envelope glycoprotein E. (SEQ ID NO: 43)

IRCIGVSNRDFVEGMSGGTWVDVVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHEHETDENRAKVEITPNSPRAEATLGGFGLDCEPRTGLDFSDLY
 YLTMNNKHHLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 20 ALAGALEAEMDGAAGRLSSGHLKCRKMDKLRRLKGVSYSLCTAAFTFTKIPAEHLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
 25 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
 LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

isol-FLR.AMM39804.1.Colombia:_Barranquilla/291-794 Flavivirus envelope glycoprotein E.
 (SEQ ID NO: 44)

IRCIGVSNRDFVEGMSGGTWVDVVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHEHETDENRAKVEITPNSPRAEATLGGFGLDCEPRTGLDFSDLY
 YLTMNNKHHLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 30 ALAGALEAEMDGAAGRLSSGHLKCRKMDKLRRLKGVSYSLCTAAFTFTKIPAEHLHGTVTVEVQYAG
 35 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
 LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

PLCal_ZV_isol-From_Vero_E6_cells.AHL37808.1.Canada/254-757 Flavivirus envelope
 glycoprotein E. (SEQ ID NO: 45)

IRCIGVSNRDFVEGMSGGTWVDVVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHEHETDENRAKVEITPNSPRAEATLGGFGLDCEPRTGLDFSDLY
 YLTMNNKHHLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 40 ALAGALEAEMDGAAGRLSSGHLKCRKMDKLRRLKGVSYSLCTAAFTFTKIPAEHLHGTVTVEVQYAG
 45 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
 LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

BeH818995.AMA12084.1.Brazil/291-794 Flavivirus envelope glycoprotein E. [Zika virus].

IRCIGVSNRDFVEGMSGGTWVDVVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHEHETDENRAKVEITPNSPRAEATLGGFGLDCEPRTGLDFSDLY
 YLTMNNKHHLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 50 ALAGALEAEMDGAAGRLSSGHLKCRKMDKLRRLKGVSYSLCTAAFTFTKIPAEHLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS

GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

H/PF/2013.AHZ13508.1.French_Polynesia/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 47)

5 IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGLDCEPRTGLDFSDLY
YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
10 ALAGALEAEMDGAAGRLSSGHLKCRCLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

PRVABC59.AMC13911.1.Puerto_Rico/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 48)

15 IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGLDCEPRTGLDFSDLY
YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
20 ALAGALEAEMDGAAGRLSSGHLKCRCLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

KU321639.1/326-829 Zika virus strain ZikaSPH2015, Brazil, Flavivirus envelope glycoprotein E. (SEQ ID NO: 49)

25 IRCIGVSNRDFVEGMSGGTWVDIVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISDM
ASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPENL
EYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGLDCEPRTGLDFSDLYL
TMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTAL
AGALEAEMDGAAGRLSSGHLKCRCLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAGTD
30 GPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
TIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTLLM
WLGLNTKNGSISLMCLALGGVLIFLSTAVSA

ZikaSPH2015.ALU33341.1.Brazil/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 50)

35 IRCIGVSNRDFVEGMSGGTWVDIVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISDM
ASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPENL
EYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGLDCEPRTGLDFSDLYL
TMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTAL
AGALEAEMDGAAGRLSSGHLKCRCLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAGTD
40 GPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
TIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTLLM
WLGLNTKNGSISLMCLALGGVLIFLSTAVSA

103344.AMC13912.1.Guatemala/291-794 polyprotein [Zika virus].

103344.AMC13912.1.Guatemala Flavivirus envelope glycoprotein E. (SEQ ID NO: 51)

45 IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEIRSYCYEASISDM
ASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPENL
EYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGLDCEPRTGLDFSDLYL
TMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTAL
AGALEAEMDGAAGRLSSGHLKCRCLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAGTD
50 GPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
TIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTLLM
WLGLNTKNGSISLMCLALGGVLIFLSTAVSA

isol-Brazil-ZKV2015.AMD16557.1.Brazil/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 52)

55 IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE

NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGTQEGAVHT
ALAGALEAEMDGAAGRLSSGHLKCRCLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHR
5 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

KU497555.1/308-811 Zika virus isolate Brazil-ZKV2015, Flavivirus envelope glycoprotein E.
(SEQ ID NO: 53)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
10 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGTQEGAVHT
ALAGALEAEMDGAAGRLSSGHLKCRCLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHR
15 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

isol-ZJ03.AMM39806.1.China/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 54)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
20 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
ALAGALEAEMDGAAGRLSSGHLKCRCLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHR
25 GSTIGKAFEATVRGARRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

isol-FSS13025.AFD30972.1.Cambodia/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 55)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
30 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
ALAGALEAEMDGAAGRLSSGHLKCRCLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHR
35 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LVWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

isol-Z1106032.ALX35660.1.Suriname/291-794 Flavivirus envelope glycoprotein E. [Zika virus]
(SEQ ID NO: 56)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
40 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
ALAGALEAEMDGAAGRLSSGHLKCRCLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHR
45 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNNAKNGSISLMCLALGGVLIFLSTAVSA

isol-Z1106033.ALX35659.1.Suriname/291-794 Flavivirus envelope glycoprotein E. [Zika virus]
(SEQ ID NO: 57)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
50 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGSVLTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
ALAGALEAEMDGAAGRLSSGHLKCRCLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHR
55 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LMWLGLNNAKNGSISLMCLALGGVLIFLSTAVSA

isol-BeH828305.AMK49165.1.Brazil/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 58)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 ALAGALEAEMDGAAGKRLSSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
 TDGPCKVPAQMAVDTQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
 LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

isol-GD01.AMK79468.1.China/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 59)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 ALAGALEAEMDGAAGKRLSSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
 LMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

isol-Z1106031.ALX35661.1.Suriname/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 60)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 ALAGALEAEMDGAAGKRLSSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
 TDGPCKVLAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHR
 SGSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGT
 LLMWLGLNTKNGSISLMCLALGGVLIFLSTAVSA

ACD75819.1.Micronesia/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 61)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPAVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 ALAGALEAEMDGAAGKRLSSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
 LVWLGLNTKNGSISLTCLALGGVLIFLSTAVSA

KU681082.3/308-811 Zika virus isolate Zika virus/H.sapiens-tc/PHL/2012/CPC-0740,

Philippines, Flavivirus envelope glycoprotein E. (SEQ ID NO: 62)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 ALAGALEAEMDGAAGKRLSSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG
 TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
 GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLKGKIHQIFGAAFKSLFGGMSWFSQILIGTL
 LVWLGLNTKNGSISLTCLALGGVLIFLSTAVSA

isol-Zika_virus%*H.sapiens-tc*%PHL%2012%CPC-0740.AMD61711.1.Philippines/291-794
 Flavivirus envelope glycoprotein E. (SEQ ID NO: 63)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
 NLEYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
 YLTMNNKHWLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
 ALAGALEAEMDGAAGKRLSSGHLKCRLLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVTVEVQYAG

TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
GSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTL
LVWLGLNTKNGSISLTCLALGGVLIFLSTAVSA

isol-BeH823339.AMK49164.2.Brazil/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 64)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVSTTVSNMAEVRSYCYEATISDI
ASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPENL
EYRIMLSVHGSQHSGMIVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLYYL
TMNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTAVVLGSQEGAVHTAL
AGALEAEMDGAAGRLSSGHLKCRLLKMDKRLRLKGVSYSLCTAAFTFTKIPAE TLHGTVTVEVQYAGTD
GPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWHRS
TIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTLLM
WLGLNTKNGSISLMCLALGGVLIFLSTAVSA

isol-P6-740.AEN75264.1.Malaysia/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 65)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMIVNDXGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YLTMMNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHT
ALAGALEAEMDGAAGRLSSGHLKCRLLKMDKRLRLKGVSYSLCTAAFTFTKIPAE TLHGTVTVEVQYAG
TDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHXR
SGSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGT
LLVWLGLNTKNGSISLTCLALGGVLIFLSTAVSA

KU744693.1/326-829 Zika virus isolate VE_Ganxian, China, Flavivirus envelope glycoprotein E. (SEQ ID NO: 66)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTAMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMLVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YYLTMMNNKHVLVHKEWFHDIPLPWHAGAATGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVH
TALAGALEAEMDGAAGRLSSGHLKCRLLKMDKRLRLKGVSYSLCTAAFTFTKIPAE TVDGTVTVEGQY
GTDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWH
RSGSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIIGA AFKSLFGGMSWFSQILIGT
LLMWLGLNTKNGSISLMCLALGGVLIFLSTAVSG

isol-VE_Ganxian.AMK79469.1.China/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 67)

IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTAMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFACSKKMTGKSIQPE
NLEYRIMLSVHGSQHSGMLVNDTGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLY
YYLTMMNNKHVLVHKEWFHDIPLPWHAGAATGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVH
TALAGALEAEMDGAAGRLSSGHLKCRLLKMDKRLRLKGVSYSLCTAAFTFTKIPAE TVDGTVTVEGQY
GTDGPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGEKKITHHWH
RSGSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIIGA AFKSLFGGMSWFSQILIGT
LLMWLGLNTKNGSISLMCLALGGVLIFLSTAVSG

ArD157995.AHL43503.1.-/291-794 Flavivirus envelope glycoprotein E. (SEQ ID NO: 68)

ISCIGVSNRDLVEGMSGGTWVDVLEHGGCVTEMAQDKPTVDIELVTMTVSNMAEVRSYCYEASLSD
MASASRCPTQGEPSLDKQSDTQSVCKRTLGDGRWGNGCGIFGKGS�VTCCKFTCKKMPGKSIQPENL
EYRIMLPVHGSQHSGMIVNDIGHETDENRAKVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLYYL
TMNNKHVLVHKEWFHDIPLPWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTAL
AGALEAEMDGAAGRLFSGHLKCRLLKMDKRLRLKGVSYSLCTAAFTFTKVPAE TLHGTVTVEVQSAGTD
GPCKVPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHRS
STIGKAFEATVRGAKRMAVLGDTAWDFGSVGGVFNLSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTLL
VWLGLNTKNGSISLTCLALGGVMIFLSTAVSA

MR_766.ABI54475.1.Uganda/291-788 Flavivirus envelope glycoprotein E. (SEQ ID NO: 69)
 IRCIGVSNRDFVEGMSGGTWVDVLEHGGCVTVMAQDKPTVDIELVTTTVSNMAEVRSYCYEASISD
 MASDSRCPTQGEAYLDKQSDTQYVCKRTLVDGRWGNGCGLFGKGS�VTCAKFTCSKKMTGKSIQPEN
 LEYRIMLSVHGSQHSGMIVNDENRAKVEVTPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLYYLTMMN
 5 KHWLVHKEWFHDIPLWHAGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTALAGAL
 EAEMDGAKGRLFSGHLKCRKMDKRLRLKGVSYSLCTAAFTFTKVPAETLHGTVTVEVQYAGTDGPCK
 VPAQMAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSYIVIGVGDKKITHHWHRSGSTIGK
 AFEATVRGAKRMAVLGDTAWDFGSVGGVFNSLGKGIHQIFGAAFKSLFGGMSWFSQILIGTLLVWLGL
 NTKNGSISLTCLALGGVMIFLSTAVSA

10

In some embodiments, the Zika virus has polyprotein, including an envelope (E) protein, with an amino acid sequence provided by any one of SEQ ID NO: 14-69. In some embodiments, the polyprotein or E protein sequence is at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%,
 15 99.5%, 99.6%, 99.7%, 99.8% or 99.9% identical to any one of SEQ ID NOs: 2-69.

The terms "identical" or percent "identity" in the context of two or more nucleic acids or amino acid sequences refer to two or more sequences or subsequences that are the same. Two sequences are "substantially identical" if two sequences have a specified percentage of
 20 amino acid residues or nucleotides that are the same (*e.g.*, at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity) over a specified region or over the entire sequence, when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that
 25 is at least about 50 nucleotides (or 10 amino acids) in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides (or 20, 50, 200 or more amino acids) in length. In some embodiments, the identity exists over the length of a protein, such as the E protein.

For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. Methods of alignment of sequences for comparison are
 30 well known in the art. See, *e.g.*, by the local homology algorithm of Smith and Waterman (1970) Adv. Appl. Math. 2:482c, by the homology alignment algorithm of Needleman and Wunsch, J. Mol. Biol. 48:443, 1970, by the search for similarity method of Pearson and Lipman. Proc. Natl. Acad. Sci. USA 85:2444, 1988, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, Jalview and TFASTA in the Wisconsin Genetics

Software Package, Genetics Computer Group. 575 Science Or., Madison. WI), by multi sequence alignment implementation using e.g. CLUSTALW (Larkin et al., (2007).

Bioinformatics, 23, 2947-2948.) or MAFFT (Katoh & Toh 2008 Briefings in Bioinformatics 9:286-298), or by manual alignment and visual inspection (see. e.g., Brent et al., Current Protocols in Molecular Biology, John Wiley & Sons, Inc. (Ringbou ed., 2003)). Two examples of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al., Nuc. Acids Res. 25:3389-3402, 1977; and Altschul et al., J. Mol. Biol. 215:403-410, 1990, respectively.

EXAMPLES

Example 1: Production of a Zika drug substance suitable for application as a vaccine in humans and animals

Materials and Methods:

For the production of ZikaV the JEV process platform (Srivastava et al., Vaccine 19 (2001) 4557-4565; US 6,309,650B1) was used as a basis. Small changes of certain process steps were applied to adapt on ZikaV properties and to improve purity. A short summary of the process steps is outlined below (see also Figure 8a+b).

Upstream:

- Roller Bottle based Vero cell expansion (25x850cm² CellBind):
- 5% CO₂, 35°C, MEM+2mM L-Glutamine+10% FBS
- Infection with ZikaV research Master Seed Bank (rMSB) at MOI 0.01
- Virus Production without serum
- 5% CO₂, 35°C, MEM+2mM L-Glutamine
- Multiple harvests (days 2, 3, 5 and 7) with re-feed
- Sterile filtration of harvests and storage at 2-8°C until further processing

Downstream:

- Pooling of harvests and concentration by ultrafiltration (100kDa)

PAT018/EP/PR1

- Stabilization of concentrated harvest (Tris/10% sucrose) for storage if required (-80°C)
- Removal of hcDNA by Protamine Sulphate (2 mg/mL)
- Sucrose Gradient Purification (optimized three layered gradient)
- 5 • Formaldehyde Inactivation (0.02%, 22°C, 10 days), neutralization with Na-metabisulfite
- Dilution to DS antigen target content and formulation with Aluminium hydroxide (0.5mg Al/mL)

10 Definitions & Abbreviations

BSA Bovine serum albumin

HPLC High performance liquid chromatography

JEV Japanese Encephalitis Virus

MALS Multi angle light scattering

15 NIV Neutralized inactivated virus

PBS Phosphate buffered saline

rms radius Root mean square radius

RSD Relative standard deviation

SEC Size exclusion chromatography

20 SGP Sucrose gradient purified

ZikaV Zika Virus

rMSB research master seed bank

p.i. Post infection

SGC Sucrose gradient chromatography

25 PS Protamine sulfate

Zika Virus Strain H/PF/2013 was originally isolated from a 51-year-old woman (SEQ ID

NO: 13). A sample was obtained from European Virus Archive EVAg. Based on this

material, a research master seed bank (rMSB) was prepared on vero cells as the cell substrate.

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Virus growth on Vero Cells

Vero cells were grown in Eagle's minimal essential medium (EMEM) containing 10% fetal bovine serum (FBS). Roller bottle cultures of Vero cell monolayers were infected with Zika Virus Strain H/PF/2013 at a multiplicity of infection (moi) of 0.01 plaque forming units (pfu) per cell. After 2 hours of virus adsorption, the cultures were washed 3 times with PBS and fed with EMEM without FBS and incubated at +35°C with 5% CO₂. Infected Vero cell cultures were incubated until the virus titer reaches a desired level.

The culture medium was harvested at days 2, 3, 5 and 7 and were pooled from those harvest days and then centrifuged in standard centrifuge. The supernatants were then filtered. Virus culture supernatants were concentrated by TFF ultrafiltration to remove cell culture media components and reduce batch volume.

Evaluation of harvest Procedure

The current JEV harvest process has scheduled harvests on days 3, 5, 7 and 9 post infection. To mimic the JEV process roller bottles infected with ZIKV bank P4-FBS at an MOI of 0.01 in infection medium (MEM with 2% FBS + 2mM L-glutamine) for 2 hours. After removing the inoculum the cells were washed twice with PBS and 200mL production medium (MEM+ 2mM L-glutamine) was added.

After taking a sample on day 2 the first virus harvest was conducted on day 3 after infection. At this point significant higher CPE could be observed compared to cells where virus was removed on day 2. Plaque assay analysis showed that the viral titers on day 2 were in the same range as for the standard harvesting schedule. However, starting with day 3 harvest the observed titers were significantly lower correlating with the increased CPE observed compared to the standard harvest schedule. On day 5 post infection no more living cells could be observed at all and the experiment was terminated with a final day 5 harvest.

The calculated titers per plaque assay are summarized in the list below:

Log 10 PFU/mL

sample day2 7.02

harvest day 3 6.66

harvest day 5 6.26

This finding led to an optimized harvest schedule to better control of CPE and allow additional harvest day 5 and 7, see Figure 19. For both harvest days the optimized ZikaV

protocol yield significant higher virus titers compared to the modified protocol showing that the time of the first harvest is crucial for production yields. Additionally first harvesting at day 3 results in maximum 2 harvest points whereas first harvesting at day 2 allows for 4 harvest points further increasing the yield gain.

5

Downstream Purification of Zika virus

The purification process was carried out at room temperature (18-22 °C) unless stated otherwise. Virus purification started with concentration of filtered combined harvest using 100 kDa cut-off TFF ultrafiltration modules to remove cell culture media components and reduce batch volume. After concentration, the pooled filtered harvest material was adjusted to a final concentration of 25 mM Tris pH 7.5 and 10% sucrose (w/w) using stock solution of both components (see Figure 9 for SEC_HPLC of different harvests prior to PS treatment). This allowed for freezing the concentrated harvest at <-65°C if required.

Host cell DNA and protein reduction as well reduction of non-infectious virus aggregates in the concentrated material was achieved by precipitation with protamine sulphate (2 mg/mL) followed by sucrose density centrifugation (2-8°C) as final polishing step (see Figure 10 for SEC_HPLC of different harvests post PS treatment). The purification process was designed to be completed within 2 working days with SGC starting on end of day 1 followed by fractionation and SDS-PAGE analysis on day 2. The sucrose gradient fractions were stored at 2-8 °C during the SDS-PAGE analysis (Silver staining) to identify the pure fractions containing ZikaV (see Figure 12). After pooling the relevant fractions, the pool was diluted and inactivated by Formalin. After pooling the relevant fractions of sucrose gradient centrifugation, the pool was diluted 1:3 in PBS and inactivated by Formalin (0.02% v/v, 200ppm). Fractions were subjected to analysis by SDS-PAGE.

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Effect of PS treatment on virus recovery

Samples of individual 30x concentrated harvests day 2, 3, 5 and 7 were analysed before and after PS treatment by SEC-HPLC and plaque assay. SEC-HPLC was used for determination of relative total ZikaV content (active + inactive) expressed as peak area, whereas the rel. ZikaV peak purity is given as relative content of virus monomer population to total virus peak. Plaque assay states the content of total active virus particles in each sample. Experimental results are summarized in Table 1. The virus peak recovery by SEC.

HPLC was only between 12 to 36% with peak purity after PS treatment in the range of >90% (no virus aggregates detected). The recovery of active virus particles by plaque assay was all > 100% (130-700%, range within the variability of the assay) showing that no active virus particles were lost during PS treatment. These results show that during PS treatment only non-infective (immature and/or aggregated virus) particles were removed.

Table 1: ZikaV Recovery by SEC-HPLC and Plaque assay before and after PS treatment.

SEC-HPLC

	Peak area mAU*min			
Harvest day	30x conc	30x +PS	SEC Recovery (%)	rel. virus monomer content after PS (%)
Day 2	101.36	18.63	18	89%
Day 3	144.51	17.48	12	90%
Day 5	19.97	5.92	30	96%
Day 7	68.80	24.43	36	99%

Plaque Assay

	PFU/mL		
Harvest day	30x conc	30x +PS	Plaque Recovery (%)
Day 2	3E+08	5E+08	179
Day 3	2E+08	4E+08	193
Day 5	1E+08	9E+08	700
Day 7	3E+08	4E+08	132

Sucrose gradient centrifugation

The PS treated harvest was split in two parts and loaded on two centrifuge bottles.

Sucrose density gradient centrifugation (SGC) was used for final concentration and polishing of the ZikaV material. The ZikaV PS treated concentrated harvest was loaded on top of a solution consisting of three layers of sucrose with different density. The three sucrose layers were selected based on a preliminary study which showed the formation of a linear sucrose gradient and complete separation of the virus particles from residual contaminants as demonstrated for ChikV, see Figure 13. The optimal volumes of the sucrose solutions were

determined empirically. The volumes of individual layers for a centrifugation in 100 mL bottle scale are shown in Table 2.

Table 2: Individual layers/volumes for a centrifugation in bottle

~40 mL PS treated harvest load Load

15 mL 15 % Sucrose solution J

15 mL 35 % Sucrose solution I

20 mL 50 % Sucrose solution H

90 mL total volume

The sucrose gradient bottles were prepared by stratifying the individual sucrose layers. A plastic tube was attached to peristaltic pump tubing. The plastic tube was mounted on a laboratory stand using a clamp and placed into the centrifuge bottle. The nozzle of the plastic tube was touching the bottom of the bottle (see Figure 11). Using a peristaltic pump the ZikaV material and the sucrose solutions were pumped into the cylinder. A measuring cylinder was used as feed vessel. The first solution pumped was the ZikaV material as it represented the solution of lowest density (10 % sucrose (w/w)). After the ZikaV material the sucrose solutions were pumped in ascending order starting with the 15 % (w/w) solution J, followed by 35 % sucrose solution I and finishing with the highest density sucrose solution H (50 % (w/w)). The described setup is shown in Figure 11. After all sucrose solutions were transferred the plastic tubing was carefully removed in order not to disturb the layers.

Prior to centrifugation the centrifuge was pre-cooled to 4 °C. The prepared SG bottles were carefully transferred into the pre-cooled rotor (Note: Sudden movement of the bottles during transfer to the rotor must be avoided in order not to disturb the sucrose layers). The bottles were centrifuged at ~11.000 RCF max at 4 °C for at least 20 hours, no break/deceleration activated. In case a different centrifuge system with a different rotor is used the necessary speed and centrifugation times need to be calculated based on the k-factor in order to achieve comparable centrifugation efficiency.

Harvesting of the sucrose gradient was done manually using a peristaltic pump. A plastic tube attached to peristaltic pump tubing was used for harvesting the sucrose gradient. The bottle containing the gradient was mounted onto a laboratory stand in a tilted position

(~12°) using a clamp. The plastic tubing was then placed into the bottle touching the bottom edge of the bottle and was fastened in position using a clamp. This resulted in a small gap of 1-2 mm between the tubing inlet and the bottom of the bottle.

Using a peristaltic pump set to a flow rate of 30 mL per minute the gradient was harvested and manually split into 2 mL fractions. A total number of 32 fractions per bottle were harvested (~ 64 mL) and the remaining volume was discarded. The fractions were immediately tested by SDS-PAGE / silver stain to identify the virus containing fractions with sufficient high purity. Representative SDS-PAGE is shown in Figure 12. Fraction 10-14 were pooled and further processed.

The purified viral solution was inactivated by incubation with 0.02% formaldehyde over a period of ten days in a 22°C controlled-temperature incubator. The formaldehyde is neutralized by addition of sodium metabisulphite on the tenth day.

The sucrose gradient pool (~17mL after sampling) was further diluted 3-fold with PBS to a final volume of 51mL in a PETG container. A volume of 1% formaldehyde (10.000ppm) solution equivalent to 1/50 of the final volume of the pre-formaldehyde pool was added to this pool resulting in an effective concentration of 200ppm. The formaldehyde-treated solution was mixed on a magnetic stirrer for 10 minutes. After sampling, the formaldehyde-treated viral solution was placed within a cooled incubator at 22°C ± 2°C. On Day 5 post addition of formaldehyde, the formaldehyde-treated viral solution was filtered through a 0.2 µm filter and then placed in the incubator at 22°C ± 2°C again. On Day 10, after removing the 10-Day inactivation final sample, a volume of 1 % (of the weight of the final formaldehyde-treated viral solution) of 200 mM-sodium metabisulphite solution (2mM final concentration) was aseptically transferred into the PETG container containing the formaldehyde-treated viral solution. After mixing for 5 minutes on a magnetic stirrer, the neutralized inactivated viral solution is held at room temperature (20 to 25°C) for a minimum of 30 minutes. After sampling, the neutralized inactivated viral solution is stored at 5°C ± 3°C until further processing.

Inactivation by formaldehyde

Critical parameters for this step are final formalin concentration, temperature, mixing and transfer into a new container. A preliminary acceptance criteria for maximum pfu/mL (determined by plaque assay) has been set on the diluted pool pre formaldehyde treatment.

The quality of the neutralized inactivated viral solution is monitored by the following parameters: Plaque assay on Day 10, SEC-HPLC, SDS-PAGE/Western Blot.

Interestingly, SEC-HPLC analysis of samples taken during the inactivation period followed by neutralization with bisulfite showed more or less constant peak area throughout the inactivation period. This is in contrast to JEV where losses of viral particles up to 60% are observed using the process disclosed by Srivastava et al. Vaccine 19 (2001) 4557-4565. In a scale-down model the viral losses were even much higher due to surface/area ratio at smaller scale and high losses due to unspecific adsorption. Differences of the ZikaV inactivation experiment and JEV inactivation were noticed as follows:

A) Much higher purity of ZikaV SGP pool with regard to residual PS ($<2\mu\text{g/mL}$) compared to JEV. The 3-fold ZikaV inactivated sample contained therefore $<<1\mu\text{g/mL}$ of residual PS. Commercial JEV SGP pool contains on average $\sim 120\mu\text{g/mL}$ (up to $152\mu\text{g/mL}$ possible). The average dilution to inactivation solution of ~ 14 -fold results in a residual PS content up to $\sim 11\mu\text{g/mL}$. It may be that higher amount of residual PS could cause virus precipitation due to cross-linking / reaction with formalin.

B) ZikaV inactivation sample contained $\sim 10\%$ sucrose (3-fold dilution of SGP pool containing ~ 30 - 35% sucrose). Sucrose might have stabilizing effect of viral ZikaV particles during treatment with formalin.

Dilution to DS and Formulation with Aluminium hydroxide (DP)

For preparation of ZikaV drug substance used in mouse potency assay an antigen content (expressed as total viral particles or SEC peak area) of 5 times higher compared to Ixiaro was targeted. The basis for determination of antigen content was SEC-HPLC. In short, a Superose 6 10/300 Increase column (GE Healthcare) equilibrated with PBS + 250 mM NaCl, pH 7.4 at 1 ml/min and 25 °C, is used to detect ZikaV at 214 nm detection wavelength in harvest samples and throughout the downstream process. In the current JEV process the antigen content in NIV is determined by a specific ELISA. A good correlation was observed between antigen content determined by ELISA and SEC-HPLC. On average, the antigen content in commercial NIV samples is in the range of 33 AU/mL corresponding to $\sim 5.2\text{mAU}$ JEV peak area, see Figure 14.

ZikaV NIV day10 (Zika peak ~36 mAU, analysed on Waters HPLC/Superose6 Increase column) was diluted with PBS to a target of 6.3 (~5.7x dilution). Aluminium hydroxide was added to a final concentration of 0.5 mg/mL Aluminium (1/20 v/v Alum 2% stock solution added) to prepare ZikaV Drug Product (DP). The DP was gently mixed for 5 min. An aliquot of the DP was removed, Alum sedimented by centrifugation and the clear supernatant analysed by SEC-HPLC. No ZikaV peak was detected in the supernatant indicating complete adsorption (estimated as >95%) of viral particles on the mineral adjuvant. Formulated ZikaV DP was stored at 2-8°C.

The impurity profile of the inactivated Zika virus DS is comparable to the profile of JEV DS with the exception of a lower PS content (Table 3).

Table 3: Determination of impurity profile in Zika and JEV DS samples:

	Specification (JEV DS)	JEV	Zika
HCP (ng/mL)	<100 LOQ 12 ng/mL	<LOQ	<LOQ
DNA (pg/mL)	<200 LOQ 40 pg/mL	<40	<40
Aggregates by SEC-MALLS (%)	Not specified, part of characterization LOQ 5%	<LOQ	<LOQ
PS (µg/mL)	Specification only at SGP pool to demonstrate consistent process performance (19-152µg/mL), *PS content in DS calculated based on PS content in SGP pool (~100 µg/mL) and average dilution factor (~28x) to DS; LOQ 2µg/mL	~4*	<<LOQ

*Typical PS impurity in a JEV sample produced in accordance with protocol disclosed in Srivastava et al. Vaccine 19 (2001) 4557-4565

SEC-MALLS Results

A representative SEC-HPLC elution profile of ZikaV NIV at 214 nm detection wavelength is shown in Figure 20. Note that BSA (50µg/mL) was added to the sample to minimize

losses in HPLC glass vial due to unspecific surface adsorption. ZikaV monomer content was estimated as ~98% with a multimer content of ~2%.

SEC-MALLS analysis (Figure 21) of the sample confirmed the radius R_z of the monomer ZikaV population peak 1 as 21.6nm and ~49nm for the multimer peak 2.

- 5 Cumulative particle size distribution showed that 89% of all viral particles are within a radius range between 18 to 25nm (Figure 22).

Results confirm purity and homogeneity of ZikaV NIV.

Viral titer by plaque assay

- 10 Active ZikaV was analyzed by plaque assay throughout the process.

Sample	Pfu/mL
Harvest day 2 (filtered)	6.4×10^7
Harvest day 3 (filtered)	1.0×10^8
Harvest day 5 (filtered)	1.5×10^8
Harvest day 7 (filtered)	1.1×10^8
PS treated harvest 300x concentrate (=SGP load)	9.0×10^8
SGP pool	8.9×10^8
Inactivation start (SGP pool 1:3 diluted)	3.4×10^8
Inactivation day 5	<LOD
Inactivation day 10	<LOD

- 15 Comparison of PS and Benzonase on process performance

- A direct comparison of DNA removal method of concentrated ZikaV harvest pool was done. One aliquot was treated with PS (2mg/mL, 15min at room temperature), the other aliquot was treated with Benzonase (50 U/mL, 2 mM MgCl₂, 4h RT, 48h 2-8°C). Both samples were further purified by sucrose gradient as described in this report. Interestingly,
- 20 the Benzonase treated samples did not sure any pure fractions after sucrose gradient centrifugation of the treated ZikaV harvest. In those fractions where the specific virus bands were detected, a high amount of host cell proteins was detected throughout the collected fractions. The PS treated material resulted in pure ZikaV containing fractions as expected. This finding may suggest that PS is not only effective for DNA removal by precipitation; in
- 25 addition it improves the recovery of virus particles in the gradient by disrupting interaction of

DNA (fragments) and virus particles. Benzonase treatment does not remove DNA, it only results in its fragmentation. Residual DNA fragments might still interact with virus particles and residual HCPs resulting in cross-contamination and co-purification in the sucrose gradient. Pooled SGP fractions were also analysed by SEC-HPLC. Although a large peak was detected, SDS-PAGE confirmed that this sample was highly contaminated with HCPs. A large peak might be detected at UV214 and 280nm after SEC-HPLC analysis due to possible interaction of HCPs with large virus particles, changing the UV absorbance.

Immunogenicity of Vero grown Zika virus

The immunogenicity of inactivated Zika virus preparations is assessed using a mouse model of Zika infection. Groups of adult mice are immunized subcutaneously (s.c.) with 500, 50, or 5 ng of inactivated Zika virus with adjuvant (*e.g.* aluminium hydroxide with or without IC31®), or without adjuvant. An additional group of mice receive PBS as a negative control. Each group is administered the indicated inoculum at t=0 and in some cases also at three to four weeks later (t=3/4). Beginning approximately three weeks after administration of the last immunization, serum samples are obtained from each of the mice at regular intervals. The serum samples are tested for the presence of neutralizing antibodies using PRNT.

The *in vivo* protective efficacy of the inactivated Zika virus preparations is also assessed using a mouse model of Zika infection, *i.e.* IFN-alpha/beta receptor knock-out mice (A129) (see *e.g.* Dowall et al., 4. March 2016, <http://dx.doi.org/10.1101/042358>) or blocking of the IFN-alpha/beta receptor by administration of anti-IFN-alpha/beta receptor monoclonal antibodies to C57BL/6 or BALB/c mice (see *e.g.* Pinto et al., 7. December 2011, DOI: 10.1371/journal.ppat.1002407). For protection assays, groups of 10 three- to eight-weeks-old A129, C57BL/6 or BALB/c mice are inoculated subcutaneously in the hindquarters with inactivated Zika virus with adjuvant (aluminium hydroxide) or without adjuvant at t=0. Age-matched controls are inoculated with PBS or non-specific antigens in alum. Mice are optionally boosted with a second administration of the indicated inoculation three to four weeks later. The mice are then challenged subcutaneously at three to eight weeks post immunization by inoculation with a deadly dose of live Zika virus. One day prior to challenge of C57BL/6 and BALB/c mice, they are passively administered (intraperitoneally) with anti-IFN-alpha/beta receptor monoclonal antibodies. Challenged mice are monitored daily for

morbidity and mortality for up to twenty-one days. Another alternative is to challenge intracranially adult vaccinated/non-vaccinated adult mice and observe protection.

It is expected that the Zika virus produced by the process of the invention will provide very similar functional read-outs in *in vitro*, *in vivo* and finally human trials as the currently licensed JEV vaccine in the EU and US and elsewhere, IXIARO®. The dosage may alter but due to the very similar impurity profile and almost identical manufacture, a very similar efficacy and safety result will be expected as was determined for the currently licensed JEV vaccine (licensed in the EU and US and elsewhere).

Discussion & Conclusion

The existing manufacturing platform for production of inactivated JEV vaccine IXIARO® was used as a basis for a manufacturing feasibility study of inactivated ZikaV vaccine candidate (Asian strain H/PF/2013). The virus was produced on vero cells cultivated in roller bottles. The virus was purified by PS treatment followed by an optimized sucrose gradient. Inactivation was done by formalin treat (0.02 %, 10 days at 22 °C). For exploratory immunization studies in mice, a DP formulated with Alum was prepared with an estimated 5-fold higher virus particle content compared to IXIARO®, the commercial JEV Vaccine. The impurity profile of the DS met all criteria as defined in the specification for IXIARO®, the commercial JEV Vaccine.

Example 2: Development of a purification process for live attenuated Chikungunya virus vaccine produced in Vero cells

A downstream process was developed for the purification of infectious Chikungunya virus particles whereby non-infectious virus particles and aggregates are removed by the addition of protamine sulphate. The unexpected and novel purification properties of protamine sulphate (PS) were evaluated in purification processes for Chikungunya Virus (ChikV) as follows:

A downstream purification process for the attenuated Chikungunya virus mutant “Δ5nsP3” (as described by Hallengård et al., 2014, supra) produced under standard cell culture conditions in Vero cells was developed. Briefly, the downstream process consists of

crude harvest filtration followed by concentration and diafiltration on a tangential flow filtration (TFF) system. DNA and host cell proteins were reduced by precipitation with protamine sulphate and by batch adsorption, respectively. Sucrose density gradient centrifugation was done as a final polishing step. Out of 16 roller bottles 1×10^{12} total PFU were purified with an overall DSP process yield of 10 - 15 % (~1 log₁₀ TCID₅₀ loss). Sucrose gradient pool samples were characterized with regard to product-related impurities, such as hcDNA, HCP and endotoxins and met safety criteria.

Harvest of Vero cell culture medium containing ChikV Δ5nsP3

ChikV Δ5nsP3 was grown on Vero cells in roller bottles. A first harvest was performed after 24 hours post infection (hpi; day 1 harvest) and stored at 2-8°C until further processing. After the first harvest, fresh medium was added and the roller bottles were returned to the incubator. A second harvest was done after 48 hours post infection (day 2 harvest) and stored at 2-8 °C.

Filtration of crude cell culture harvest

At both harvest timepoints the crude harvest was immediately filtered using a 0.2 μm filter capsule (GE ULTA™ CG, 2 inch). The filtered harvest after 48 hpi was pooled together with the 24 hpi harvest and the pooled filtered harvest material was immediately further processed by ultrafiltration.

Purification of ChikV Δ5nsP3 by tangential flow filtration (TFF)

The pooled filtered harvest material was further processed by tangential flow filtration (TFF) in order to concentrate the harvest, reduce host cell proteins and replace the depleted cell culture medium with a defined buffer system (buffer exchange). A Millipore TFF system (Millipore Pellicon II mini membrane holder) equipped with a 100 kDa cutoff PES membrane module (Pellicon2 Biomax, 1000 cm²) was used for concentration and buffer exchange. A Pellicon2 Biomax membrane module was mounted on the Pellicon II mini filter holder and the device was connected to a peristaltic pump. The system was first rinsed with ultra-pure water and then sanitized by recirculation of 0.1 M NaOH for 60 min. In case the system was not used immediately, it was stored in 0.1 M NaOH until use. Prior to use the

system was rinsed with 1 L of RO-water followed by buffer A until the permeate pH value was constant at $\text{pH } 7.4 \pm 0.2$.

Adjustment of the ChikV $\Delta 5\text{nsP3}$ harvest (pH, salt)

The pooled filtered harvest material was adjusted to a final concentration of 25 mM Tris and 150 mM NaCl using stock solutions of both components (see Table 1). This adjustment was done to increase buffering capacity and to reduce unspecific adsorption to the membrane. The necessary volumes of stock solutions D (1 M Tris, pH 7.4) and E (4.5 M NaCl) were calculated as follows:

Volume of stock solution D (1 M Tris, pH 7.4) added to pooled harvest = Volume of pooled filtered harvest / 40

Volume of stock solution E (4.5 M NaCl) added to pooled harvest = Volume of pooled filtered harvest / 30

4 L harvest obtained from 20 RB (850cm²) would require addition of 100 mL stock solution D (1 M Tris, pH 7.4) and 133 mL stock solution E (4.5 M NaCl).

The calculated volumes of stock solution D and Buffer E were added to the pooled filtered harvest under gentle stirring. The adjusted harvest was then stirred using a magnetic stirrer for 5 minutes at room temperature.

Concentration and diafiltration of the ChikV $\Delta 5\text{nsP3}$ harvest by TFF

In a first step the adjusted harvest material was concentrated approximately 10 fold. The feed flowrate was approximately 220 mL/min. The transmembrane flux at a transmembrane pressure of approximately 0.6 bar was in the range of 90 ± 5 mL/min per 1000 cm² membrane. After concentration, the cell culture medium was exchanged against 25 mM Tris, 150 mM NaCl, pH 7.5 by continuous diafiltration with 6 volume exchanges. The diafiltration buffer was supplied to the feed vessel from a measuring cylinder by a second peristaltic pump set to a flowrate of approximately 90 mL/min. Minor flowrate adjustments of the second peristaltic pump in the range of ± 10 mL/min were done manually to ensure a constant volume of harvest in the feed vessel. After 6 volume exchanges, diafiltration was stopped. The liquid remaining in the membrane module was recovered by pumping the module empty with air.

Sucrose addition to diafiltrated ChikV Δ5nsP3 material

5 After diafiltration, sucrose stock solution H (50% (w/w) sucrose solution) was added to the diafiltrated material to achieve a final sucrose concentration of 10% (w/w). The volume of buffer H was calculated as follows:

Volume of stock solution H added (mL) = Volume (mL) of diafiltrated ChikV material x 0.25 (dilution factor = 1:4) (i.e., final sucrose concentration is 10%)

10 Example: 400mL diafiltrated ChikV solution would require addition of 100mL stock solution H (50% sucrose).

 The calculated volume of solution H was added to the diafiltrated ChikV Δ5nsP3 material under gentle stirring and the solution was then stirred using a magnetic stirrer for a further 5 minutes at room temperature. (At this stage of the process the material can be either
15 immediately further processed or stored frozen (< -65°C, hold step).)

DNA reduction by protamine sulphate precipitation

 A DNA precipitation step using protamine sulphate (PS) was performed to reduce hcDNA. Protamine sulphate stock solution L (50 mg/mL PS in PBS) was added to the
20 diafiltrated ChikV Δ5nsP3 material to a final nominal concentration of ~1.6 mg/mL. The necessary volume of stock solution L was calculated as follows:

Volume of stock solution L (50 mg/mL PS) added = Volume of diafiltrated ChikV Δ5nsP3 material in 10% sucrose / 31

 Example: 500 mL diafiltrated ChikV Δ5nsP3 solution in 10% sucrose would require
25 addition of 16 mL stock solution L (50 mg/mL PS in PBS).

The protamine sulphate stock solution was added while stirring the ChikV Δ5nsP3 material using a magnetic stirrer followed by incubation at 2-8°C for 30 minutes. After incubation, the DNA precipitate was not removed. The material was immediately further processed by batch adsorption with Capto™ Core 700 chromatography media.

30 Batch adsorption with Capto™ Core 700

 To reduce HCPs, a batch adsorption step with Capto™ Core 700 (CC700) chromatography medium was performed after DNA precipitation. CC700 slurry (50% slurry

in buffer A) was added directly to the protamine sulphate treated material. The required slurry volume was determined based on the volume of ChikV harvest material (d1+d2) and was calculated as follows:

Volume of CC700 slurry added to PS-treated concentrated harvest (mL) = Volume of
 5 ChikV Δ5nsP3 harvest material (mL) x 0.02 (dilution factor = 1:50) (i.e., final concentration of CC700 is 1%)

After slurry addition, the material was incubated at 4°C for 15 minutes under constant agitation using a magnetic stirrer. After incubation, the CC700 solid matter was allowed to settle by gravity for 10 minutes. The ChikV Δ5nsP3 material was then removed from the top
 10 of the solution in order to avoid blocking of the filter by the CaptoCore particles. The remaining CaptoCore particles and the DNA precipitate were then removed from the solution by filtration using a 0.2 μm Mini Kleenpak EKV filter capsule (Pall). The resulting filtrate was further processed by sucrose density gradient centrifugation.

15 Sucrose density gradient centrifugation

Sucrose density gradient centrifugation (SGC) was used for final concentration and polishing of the ChikV Δ5nsP3 material. The ChikV material was loaded on top of a solution consisting of three layers of sucrose with different densities. The three sucrose layers were selected based on a preliminary study which showed the formation of a linear sucrose
 20 gradient and good separation of the virus particles from residual contaminants. The optimal volumes of the sucrose solutions were determined empirically. The volumes of individual layers for a centrifugation at 500 mL scale are shown in Table 3.

Table 3. Sucrose concentrations and volumes (500 mL scale).

25	Solution	Volume (mL)
	Harvest with 10% sucrose	360
	15% sucrose	40
	35% sucrose	40
	50% sucrose	60
30	Total volume	500

Preparation of the sucrose gradient

The sucrose gradient bottles (500 mL) were prepared by underlaying the individual sucrose layers. A 3.5 mm ID plastic tube was attached to 60 cm of peristaltic pump tubing. The plastic tube was mounted on a laboratory stand using a clamp and placed into the centrifuge bottle. The nozzle of the plastic tube was touching the bottom of the bottle. Using a peristaltic pump set to a flow rate of 25 mL per minute, the ChikV Δ 5nsP3 material and the sucrose solutions were pumped into the cylinder. A measuring cylinder was used as a feed vessel. The first solution pumped was the ChikV Δ 5nsP3 material as it had the lowest density (10% sucrose (w/w)). Following the addition of the ChikV Δ 5nsP3 material, the sucrose solutions were pumped in ascending order starting with the lowest (15%), followed by the 35% sucrose solution and finishing with the highest density sucrose solution (50%). After all sucrose solutions were transferred, the plastic tubing was carefully removed in order not to disturb the layers.

Centrifugation

Prior to centrifugation a Beckman Avanti JXN-26 centrifuge equipped with rotor Beckman 10.500 was pre-cooled to 4°C. The prepared SG bottles were carefully transferred into the pre-cooled (4°C) rotor so as to not to disturb the sucrose layers. The bottles were centrifuged at 10,000 rpm (~18,500 rcf) at 4°C for 17-20 hours. (In case a different centrifuge system with a different rotor would be used, the necessary speed and centrifugation times would need to be calculated based on the k-factor in order to achieve comparable centrifugation efficiency.)

Sucrose gradient harvest

Harvesting of the sucrose gradient was done manually using a peristaltic pump. A 3.5 mm ID plastic tube attached to 60 cm of peristaltic pump tubing was used for harvesting the sucrose gradient. The 500 mL bottle containing the centrifuged gradient was mounted onto a laboratory stand in a tilted position (~12°) using a clamp. The plastic tubing was then placed into the bottle touching the bottom edge of the bottle and was fastened in position using a clamp. This resulted in a small gap of 1-2 mm between the tubing inlet and the bottom of the bottle. Using a peristaltic pump set to a flow rate of 60 mL per minute, the gradient was harvested and manually split into 5 mL fractions. A third of the bottle volume was harvested

and the rest was discarded. The fractions were immediately tested by measuring UV absorbance in a plate reader as described below.

Analysis of fractions by UV absorbance and SEC-HPLC

5 UV absorbance measurement was used as primary method for analysis of the sucrose gradient fractions. Absorbance at 214, 280 and 260 nm was tested immediately after fractionation was completed. Briefly, a 100 μ L sample of each fraction was transferred into a 96 well plate and absorbance at 214, 260 and 280 nm was measured using a plate reader. The absorbance values were plotted against the fraction number. The presence of impurities was
10 indicated by an increase of the UV214 signal after the main peak. The fractions comprising the main peak were pooled from the peak start to the valley of the 214 nm curve. This method can be used as single method for pooling ChikV Δ 5nsP3 fractions.

After identification of the virus containing fractions, the respective fractions were pooled. Pooling criteria for SGC fractions were based on UV 260 nm data, e.g. start of
15 pooling at ~10% of peak maximum, end of pooling at ~30% of peak maximum. (Final pooling criteria at a manufacturing scale may need to be determined empirically.) The sucrose gradient pool was either stored at $< -65^{\circ}\text{C}$ or immediately further formulated to drug substance (DS).

Size exclusion chromatography

20 The final pooled SGC fractions containing purified infectious ChikV Δ 5nsP3 virus particles were analyzed for purity by SEC-HPLC. In brief, SEC was performed as follows: a Superose 6 10/300 Increase column (GE Healthcare) equilibrated with PBS + 250 mM NaCl, pH 7.4 at 1 ml/min and 25°C , was used to detect ChikV particles at 214 nm detection
25 wavelength in the pooled samples. SEC-HPLC is a semi-quantitative (relative yield) and qualitative (purity) method that separates intact virus particles from virus aggregates and host cell proteins (HCPs). The method cannot distinguish between infectious and non-infectious virus particles due to their identical retention time.

Two defined peaks were identified by SEC: the ChikV Δ 5nsP3 peak and a peak
30 corresponding to buffer components. The SGC step yield based on SEC-HPLC data for pooled fractions F6-F11 was estimated at ~70 %. The final purity of the ChikV Δ 5nsP3 SGC pool, based on SEC-HPLC analysis, was estimated at $>95\%$.

SDS-PAGE and silver stain

SDS-PAGE silver stain was performed in order to qualitatively assess sample purity throughout the purification process from the first crude harvest through SGC. Briefly, ChikV process samples analyzed by SDS-PAGE/silver stain were diluted 1:1.33 with LDS buffer and were heated to 70°C for 5 minutes. The samples were loaded onto 4-12 % Bis-Tris Gels (NuPAGE). Silver staining was done using the Silver Express staining kit (Invitrogen).

A silver-stained gel of a representative ChikV Δ5nsP3 purification is shown in Figure 15. The viral proteins E1, E2 and C are marked on the right-hand side of the gel. The final SGC pool (fraction 7-fraction 11) is shown in lane 12. Note that a defined HCP band migrating between ChikV protein E2 and C still appears after CaptoCore700 treatment that has been identified as a single band in SDS-PAGE. This impurity is removed by sucrose gradient centrifugation, but can still be seen in fractions 13 and 14 (corresponding to lanes 14 and 15 of Figure 15).

Enrichment of infectious ChikV Δ5nsP3 particles by PS treatment

Although generally used as a method of removing contaminating hcDNA, it was observed in the course of the present invention that PS treatment also removes virus aggregates and HCPs. Size exclusion chromatography (SEC-HPLC, as described above) was used to throughout the purification process to determine the purity of the ChikV virus relative to impurities which also generate UV absorption.

As can be seen in Figure 16a, treatment with PS reduces not only host cell proteins and low molecular weight contaminants of the ChikV Δ5nsP3 preparation, but also reduces the SEC area corresponding to virus products, including aggregates as indicated. A surprising finding, however, was that even a reduction of the total SEC area by 86% (in a representative experiment shown in Fig. 16B, grey portion of bars) did not result in a concomitant reduction in infectious virus particles as measured by TCID₅₀ (left axis). Instead, even though a large percentage of virus particles were removed by PS treatment, the infectious particles were not. This observation indicates that PS treatment selectively enriches infectious virus particles from a larger pool of total virus particles present in the crude harvest.

TCID50 was performed to quantify infectious virus particles during the course of the purification process and to assign an active virus titer to final drug substance and drug product samples. Briefly, Vero cells were seeded at 2×10^4 cells per well in 100 μ L medium (EMEM with 2 mM L-Glutamine + 5 % FBS (+ 1 % antibiotic/antimycotic) in 96-well TC-treated flat-bottom plates and incubated overnight at 35°C / 5% CO₂. On day two, Vero cell monolayers were infected by adding 100 μ L of 1:10 serial dilutions of test samples to each of quintuplicate wells seeded with Vero cells and incubated at 35°C / 5% CO₂. On day seven, plaques were counted by visualization under a microscope. The TCID50 was calculated according to the Reed & Munch endpoint calculation method (Reed, L.J.; Muench, H. (1938) A simple method of estimating fifty percent endpoints" The American Journal of Hygiene 27: 493–497).

Furthermore, electron microscopy of ChikV samples before and after PS treatment showed that not only large aggregates but also smaller non-infectious virus-like particles (basically not fully assembled particles without RNA genome) are effectively removed by PS.

Furthermore, this enrichment of infectious virus particles could also be observed when analyzing day one and day two crude harvests separately. As presented in Table 4, the SEC area (total virus particles) of the day 1 harvest remains roughly the same after PS treatment; whereas a large decrease in virus peak area is seen for the day 2 harvest. This observation was confirmed by MALLS analysis of the virus preparation, wherein it was seen that a higher percentage of virus particles were of the correct size following PS treatment. Similarly to the results shown in Fig. 16, day 1 and day 2 harvests showed no reduction in infectious particles as measured by TCID50 following PS treatment, indicating that mainly non-infectious, immature and/or aggregated virus particles are removed during the PS treatment and infectious particles are enriched in the preparation.

Table 4. Overview of the process of ChikV $\Delta 5\text{nsP3}$ purification as described in Example 1. SEC-MALLS analysis of harvests before and after PS treatment shows the removal of larger virus particles (aggregates), an effect that is particularly pronounced for day 2 harvests.

	SEC	MALLS	Infectious particles		
	Area [mAU*min]		Total particles/mL	% correct size	
5	(20-40 nm)	TCID50 log 10			
	Harvest 1 (H1)	57	1.17E+11	49%	10.2
	Harvest 1 + PS	53	1.33E+11	81%	10.0
10	Harvest 2 (H2)	36	4.60E+09	3%	7.9
	H2 + protamine sulphate	2	8.80E+09	59%	7.9
	Combined Harvests (C)	67	2.60E+10	14%	9.9
	C + protamine sulphate	24	8.00E+10	72%	10.1

15

Finally, an overview of the relative amounts of ChikV particles and other components as measured by SEC-HPLC at various steps throughout the entire virus purification process from crude harvest (a) to the final SGC purified pool can be seen in Figure 17. In sum, not only are the vast majority of contaminants and undesired products removed by the process, ChikV particles are highly purified. As shown by the previously presented data, the final preparation is a highly enriched preparation of infectious ChikV particles.

20

Drug Substance (DS) Formulation

The pooled SGC fractions are diluted with DS formulation buffer M (10 mM Tris, 5% Sucrose, 1% (10 mg/mL) rHSA, pH 7.4 ± 0.2). The final target volume of DS should be in the range of approximately 2 L. Based on current data the estimated range of the dilution factor might be 1:20 to 1:50.

25

Final DS sterile filtration

The final DS was filtered under aseptic conditions in a laminar flow hood using a sterility grade 0.2 µm syringe filter (e.g. 0.2 µm Mini Kleenpak EKV filter capsule with 220 cm² filter surface, Pall).

- 5 Quantification of host cell DNA (hcDNA) host cell protein (HCP) and endotoxin
- The residual host cell DNA content of the sucrose gradient pool samples was determined by using the qPCR based assay. The DNA content in SGC pool was determined to be ≤ 0.002 ng/mL. The presence of residual host cell protein (HCP) from Vero cells was determined by ELISA. Residual host cell proteins present in the sucrose gradient pool samples were
- 10 quantified using the Vero Cell HCP ELISA kit (Cygnus, F500). The residual host cell protein content in SGC pool was determined to be ≤ 200 ng/mL.

- Endotoxin content of the SGC pool and DS was measured by Endosafe®-PTSTM system (Charles River). The system uses LAL reagents by a kinetic chromogenic methodology to measure color intensity directly related to the endotoxin content in a sample.
- 15 Each cartridge contains precise amounts of a licensed LAL reagent, chromogenic substrate and an endotoxin control standard. Samples were diluted 1:100 in WFI. The SGC Pool F7-F11 was determined to be < 5.00 EU/mL; likewise, the Drug Substance was also determined to have < 5.00 EU/mL.

- The following specifications for impurities in final Drug product were proposed:
- 20 hcDNA < 10 ng/dose; Endotoxins < 50 EU/dose; HCP < 200 ng/dose. These residual specifications would already be met in the highly concentrated SGC pool (~10 log TCID₅₀/mL), which provides a high margin of safety considering the high dilution factor of SGC pool to final DP of > 1:1000.

Further more detailed aspects of the invention:

A1. A Zika virus vaccine comprising an optimally inactivated Zika virus particle, wherein the Zika virus particle is able to seroconvert a subject that is administered the Zika virus vaccine with at least a 70% probability.

A2. The Zika virus vaccine of claim A1, wherein the Zika virus particle is able to seroconvert the subject that is administered the Zika virus vaccine with at least a 80%, 85%, 90%, or 95% probability.

A3. The vaccine of claim A1 or A2, wherein the Zika virus particle has a RNA genome corresponding to the DNA sequence provided by any one of the nucleic acid sequences of SEQ ID NOs: 1-13, or a variant nucleic acid sequence that is at least 88% identical to any one of SEQ ID NOs: 1-13 and able to pack a virulent Zika virus.

A4. The vaccine of any one of claims A1-A3, wherein the Zika virus particle has an E protein selected from the amino acid sequences provided by any one of SEQ ID NOs: 14-69, or a variant amino acid sequence that is at least 95% identical to any one of SEQ ID NOs: 14-69 and able to pack a virulent Zika virus.

A5. The vaccine of any one of claims A1-A4, wherein the Zika virus is inactivated by chemical inactivation, thermal inactivation, pH inactivation, or UV inactivation.

A6. The vaccine of claim A5, wherein the chemical inactivation comprises contacting the Zika virus with a chemical inactivation agent to completely inactivate the Zika virus as measured by plaque assay.

A7. The vaccine of claim A6, wherein the chemical inactivation comprises contacting the Zika virus with formaldehyde.

A8. The vaccine of claim A7, wherein the formaldehyde inactivation comprises contacting the Zika virus with formaldehyde for between 2-10 days.

A9. The vaccine of any one of claims A5-A8, wherein the chemical activation is performed at about +4°C or about +22°C.

5 A10. The vaccine of any one of claims A1-A9, further comprising an adjuvant.

A11. The vaccine of claim A10, wherein the adjuvant is an aluminum salt adjuvant.

10 A12. The vaccine of claim A11, wherein the aluminum salt adjuvant is aluminium hydroxide or aluminium phosphate salt.

A13. The vaccine of any one of A10-A12, wherein the vaccine comprises or further comprises an adjuvant comprising a peptide and a deoxyinosine-containing immunostimulatory oligodeoxynucleic acid molecule (I-ODN).

15

A14. The vaccine of claim A13, wherein the peptide comprises the sequence KLKL5KLK (SEQ ID NO: 70) and the I-ODN comprises oligo-d(IC)13 (SEQ ID NO: 71).

20 A15. The vaccine of any one of claims A1-A14, further comprising one or more pharmaceutically acceptable excipient.

B1. A kit comprising a Zika virus vaccine of any one of claims A1-A15.

25 B2. The kit of claim B1, further comprising a second vaccine.

B3. The kit of claim B2, wherein the second vaccine is a West Nile virus vaccine, a Japanese Encephalitis virus vaccine, a Yellow Fever virus vaccine, a Dengue virus vaccine or a Chikungunya virus vaccine.

30

C1. A method, comprising

administering a first dose of a therapeutically effective amount of the Zika virus vaccine of any one of claims A1-A15 to a subject in need thereof.

5 C2. The method of claim C1, further comprising administering a second dose of a therapeutically effective amount of the Zika virus vaccine.

C3. The method of claim C1 or C2, wherein the second dose of the Zika virus vaccine is administered about 7 days after the first dose of the Zika virus vaccine.

10 C4. The method of claim C1 or C2, wherein the second dose of the Zika virus vaccine is administered about 14 days after the first dose of the Zika virus vaccine.

C5. The method of claim C1 or C2, wherein the second dose of the Zika virus vaccine is administered about 28 days after the first dose of the Zika virus vaccine.

15

C6. The method of any one of claims C1-C5, wherein the administering results in production of Zika virus neutralizing antibodies.

20 D1. A method of producing a Zika virus vaccine, comprising
(i) passaging a Zika virus on Vero cells, thereby producing a culture supernatant comprising the Zika virus;
(ii) harvesting the culture medium of (i);
(iii) precipitating the harvested culture medium of (ii), thereby producing a Zika virus
25 supernatant; and
(iv) optimally inactivating the Zika virus in the Zika virus supernatant of (iii) thereby producing an inactivated Zika virus.

30 D2. The method of claim D1, further comprising concentrating the culture medium of (ii) prior to step (iii).

D3. The method of claim D1 or D2, wherein the precipitating of (iii) comprises contacting the culture medium of (ii) with protamine sulfate or benzoate.

D4. The method of any one of claims D1-D3, further comprising (v) dialyzing the inactivated Zika virus of (iv), thereby producing a dialyzed Zika virus.

D5. The method of claim D4, further comprising (vi) filtering the dialyzed Zika virus of (v).

D6. The method of any one of claims D1-D5, wherein the inactivating is by chemical inactivation, thermal inactivation, pH inactivation, or UV inactivation.

D7. The method of claim D6, wherein the chemical inactivation comprises contacting the Zika virus with a chemical inactivation agent for at least 4 days.

D8. The method of claim D6 or D7, wherein the chemical inactivation agent comprises formaldehyde.

D9. The method of any one of claims D6-D8, wherein the chemical activation is performed at about +4°C or about +22°C.

D10. The method of claim D8 or D9, further comprising neutralizing the formaldehyde.

D11. The method of claim D10, wherein the neutralizing is performed with sodium metabisulfite.

E1. The use of the optimally inactivated Zika virus vaccine of any one of claims A1-A15 for the treatment and prevention of a Zika virus infection.

E2. The use of claim E1, wherein the inactivated Zika virus vaccine is administered in a first dose of a therapeutically effective amount to a subject in need thereof.

E3. The use of claim E2, wherein the inactivated Zika virus vaccine is administered in a second dose of a therapeutically effective amount to the subject.

5 E4. The use of claim E3, wherein the second dose of the inactivated Zika virus vaccine is administered about 7 days after the first dose of the Zika virus vaccine.

E5. The use of claim E3, wherein the second dose of the Zika virus vaccine is administered about 14 days after the first dose of the Zika virus vaccine.

10

E6. The use of claim E3, wherein the second dose of the Zika virus vaccine is administered about 28 days after the first dose of the Zika virus vaccine.

15 E7. The use of any one of claims E1-E6, wherein the vaccine administration results in production of Zika virus neutralizing antibodies.

F1. A pharmaceutical composition for use in the treatment and prevention of a Zika virus infection, wherein said pharmaceutical composition comprises the optimally inactivated Zika virus vaccine of any one of claims A1-A15.

20

F2. The pharmaceutical composition of claim F1, wherein the inactivated Zika virus vaccine is administered in a first dose of a therapeutically effective amount to a subject in need thereof.

25

F3. The use of claim F2, wherein the inactivated Zika virus vaccine is administered in a second dose of a therapeutically effective amount to the subject.

30 F4. The use of claim F3, wherein the second dose of the inactivated Zika virus vaccine is administered about 7 days after the first dose of the Zika virus vaccine.

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F5. The use of claim F3, wherein the second dose of the Zika virus vaccine is administered about 14 days after the first dose of the Zika virus vaccine.

F6. The use of claim F3, wherein the second dose of the Zika virus vaccine is
5 administered about 28 days after the first dose of the Zika virus vaccine.

F7. The use of any one of claims F1-F6, wherein the vaccine administration results in production of Zika virus neutralizing antibodies.

CLAIMS

What is claimed is:

1. A process of purification of infectious virus particles, comprising the steps of:
 - 5 (a) providing a crude harvest (a) comprising virus particles and impurities, wherein the impurities are generated from growing said virus particles on a cell substrate;
 - (b) reducing impurities from the crude harvest (a) by precipitation with an agent comprising protamine, preferably a protamine salt, more preferably a protamine sulphate, even more preferably a recombinant protamine sulphate, to obtain a virus preparation (b);
 - 10 (c) further purifying the virus preparation (b) by an optimized sucrose density gradient centrifugation, wherein the optimized sucrose gradient is provided such that the protamine can be completely or almost completely separated from the virus fraction; and wherein the protamine concentration is reduced by this step to the extent that the protamine concentration in the final drug substance is below 1 µg/ml, preferably below 0.5 µg/mL, more preferably
 - 15 below 0.1 µg/mL, most preferably below 0.05µg/mL.
2. The process of claim 2, wherein the virus particles are selected from the group consisting of flaviviruses, e.g. yellow fever virus or Zika virus and alphaviruses, e.g. Chikungunya.
- 20 3. The process of claim 1 or claim 2, additionally comprising the step of:
 - (d) a solid-phase matrix packed in a column comprising a ligand-activated core and an inactive shell comprising pores, wherein the molecular weight cut off of the pores excludes the virus particles from entering the ligand-activated core, and wherein a molecule smaller
 - 25 than the molecular weight cutoff of the pores can enter the ligand-activated core and collecting the virus particles.
4. The process of any of claims 1 to 3, wherein the residual host cell DNA of the virus preparation (c) is less than 10 ng/mL and the residual host cell protein of the final virus
- 30 preparation (c) is less than 100 ng/mL.

5. The process of any of claims 1 to 4, wherein the crude harvest (a) comprising virus particles and impurities is subjected to one or more pre-purification step(s) prior to step (b).

6. The process of claim 5, wherein the one or more pre-purification step(s) comprises

- 5 (a) filtration using a filter having a pore size equal to or less than 0.2 μm ; and/or
(b) digestion of host cell genomic DNA by enzymatic treatment; and/or
(c) ultra/diafiltration using a hollow fiber membrane having a pore size equal to or greater than 300 kDa, preferably equal to or greater than 100 kDa.

10 7. The process of any one of claims 1 to 6, wherein the concentration of protamine sulphate is 0.5 to 3 mg/ml, more preferably 1 to 2 mg/ml, more preferably 1.2 to 1.8 mg/ml, more preferably 1.4 to 1.6 mg/ml, most preferably 1.6 mg/ml or 2 mg/ml.

15 8. The process of any one of claims 1 to 7, wherein the enrichment of infectious virus particles in the virus preparation (c) or any final virus preparation relative to total virus products in the crude harvest (a) is in the range from at least 50% to 95%, preferably at least 80%.

20 9. The process of any one of claims 5 to 8, wherein the one or more pre-purification step(s) prior to step (b) of any of claims 5 to 8 is performed using a filter having a pore size equal to or less than 1 μm , preferably 0.2 μm .

10. The process of any one of claims 1 to 9, wherein the residual impurity of the virus preparation (c) is less than 10%.

25

11. The process of any one of claims 1 to 10, wherein the virus is propagated in a cell line selected from the group consisting of an EB66 cell line, a Vero cell line, a Vero- α His cell line, a HeLa cell line, a HeLa-S3 cell line, a 293 cell line, a PC12 cell line, a CHO cell line, a 3T3 cell line, a PerC6 cell line, a MDSK cell line, a chicken embryonic fibroblast cell line, a duck cell line, and a diploid avian cell line.

30

12. The process of claim 11, wherein said cell line is a Vero cell line.

13. The process of any one of claims 1 to 12, wherein the infectious virus particles is an infectious Zika virus particle that is a live virus, an attenuated live virus, a chimeric virus, a modified live virus, or a recombinant live virus.

5

14. The process of any one of claims 1 to 13, wherein the Zika virus is a Zika virus strain of the Asian lineage or an immunogenic variant thereof.

15. The process of any one of claims 1 to 14, wherein said process resulting in final virus preparation (c) or (d) is followed by an inactivation step, wherein the virus is inactivated preferably by formaldehyde.

10

16. Use of the process according to any one of claims 1 to 15 for manufacturing a composition for immunization against a virus infection.

15

17. The use according to claim 16, wherein the composition for immunization against a virus infection is an infection caused by a group of viruses consisting of yellow fever virus, Chikungunya virus and Zika virus.

18. A composition comprising the virus particles obtainable or obtained by the process of any one of claims 1 to 17 for treating and/or preventing an infection, such as e.g. a Zika virus infection.

20

19. A Zika virus vaccine comprising an inactivated Zika virus particle grown on vero cells, wherein the Zika virus particle is able to seroconvert a subject that is administered the Zika virus vaccine with at least a 70% probability and comprises minor amounts of protamine sulphate, preferably below the detection limit.

25

20. The Zika virus vaccine of claim 19, wherein the Zika virus particle is able to seroconvert the subject that is administered the Zika virus vaccine with at least a 80%, 85%, 90%, or 95% probability, preferably a 80% probability.

30

21. The vaccine of claim 19 or 20, wherein the Zika virus particle has a RNA genome corresponding to the DNA sequence provided by any one of the nucleic acid sequences of SEQ ID NOs: 2-13, or a variant nucleic acid sequence that is at least 88% identical to any one of SEQ ID NOs: 2-13 and able to pack a virulent Zika virus.

5

22. The vaccine of any one of claims 19, 20 and 21, wherein the Zika virus particle has an E protein selected from the amino acid sequences provided by any one of SEQ ID NOs: 14-69, or a variant amino acid sequence that is at least 95% identical to any one of SEQ ID NOs: 14-69 and able to pack a virulent Zika virus.

10

23. The vaccine of any one of claims 19, 20 to 22, wherein the Zika virus obtained by culturing on Vero cells is purified by protamine sulfate precipitation and sucrose gradient centrifugation.

15

24. The vaccine of claim 23, wherein the sucrose gradient centrifugation is an optimized sucrose gradient centrifugation.

25. The vaccine of claim 24, wherein the optimized sucrose gradient centrifugation comprises a virus comprising fraction in a 10% (w/w) sucrose solution and three layers of sucrose with different densities, i.e. a first sucrose solution with 15% (w/w) sucrose solution, a second sucrose solution with 35% (w/w) sucrose solution, and a third sucrose solution with a 50% (w/w) sucrose solution.

20

26. The vaccine of any one of claims 19, 20 to 25, wherein the Zika virus is inactivated by chemical inactivation, thermal inactivation, pH inactivation, or UV inactivation.

25

27. The vaccine of claim 26, wherein the chemical inactivation comprises contacting the Zika virus with a chemical inactivation agent for longer than is required to completely inactivate the Zika virus as measured by plaque assay.

30

28. The vaccine of claim 27, wherein the chemical inactivation comprises contacting the Zika virus with formaldehyde.

29. The vaccine of claim 28, wherein the formaldehyde inactivation comprises contacting the Zika virus with formaldehyde for between 2-10 days.
- 5 30. The vaccine of any one of claims 27-29, wherein the chemical activation is performed at about +4°C or about +22°C.
31. The vaccine of any one of claims 19 to 30, further comprising an adjuvant.
- 10 32. The vaccine of claim 31, wherein the adjuvant is an aluminum salt adjuvant.
33. The vaccine of claim 32, wherein the aluminum salt adjuvant is aluminium hydroxide or aluminium phosphate salt.
- 15 34. The vaccine of claim 32, wherein the aluminum salt adjuvant is aluminium hydroxide with less than 1.25ppb Cu based on the final pharmaceutical composition comprising the Zika virus, preferably the inactivated Zika virus.
- 20 35. The vaccine of any one of claims 19 to 34, further comprising one or more pharmaceutically acceptable excipient.

ABSTRACT

Described herein are improved purification methods for virus vaccines and compositions. Also described are Zika vaccines and methods of producing and administering
5 said vaccines to subjects in need thereof.

Figure 1

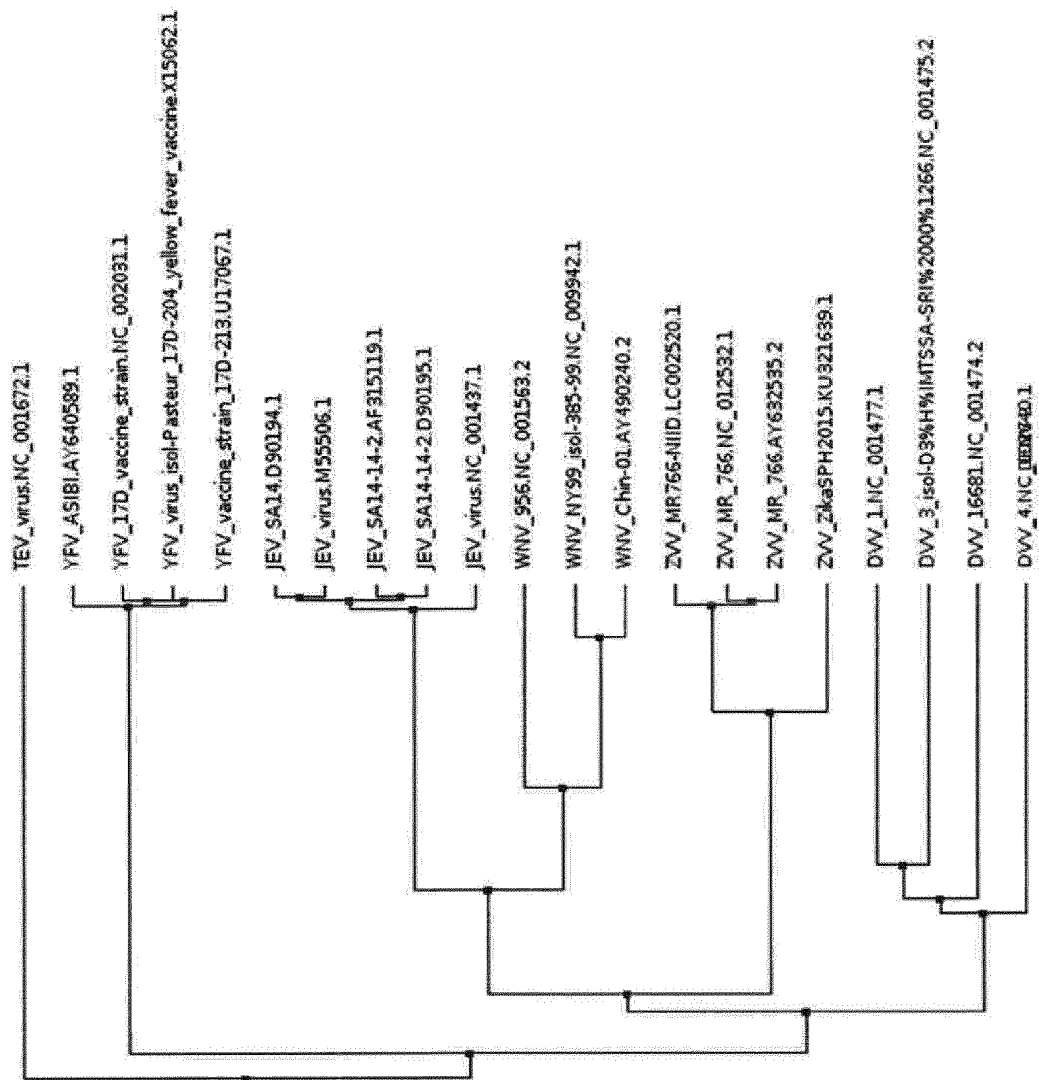


Figure 2

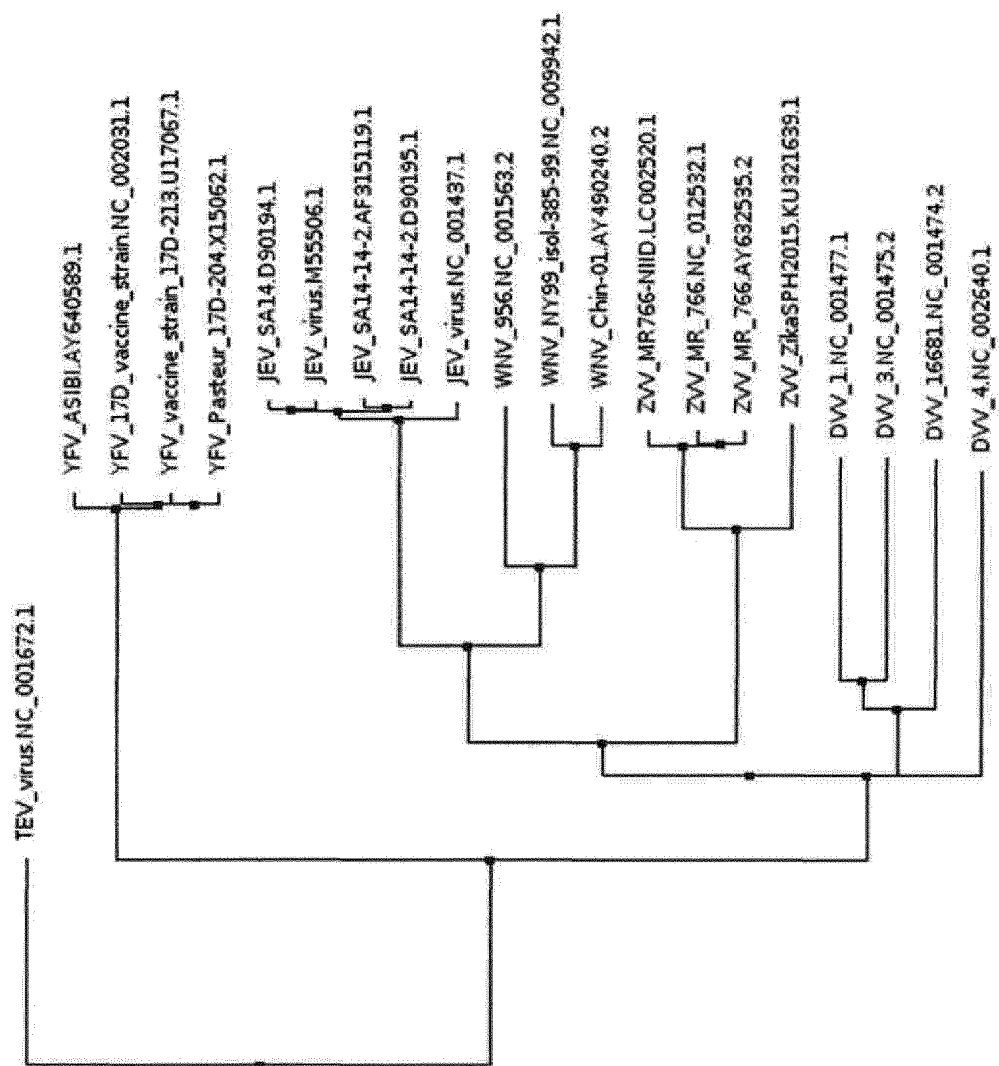


Figure 3

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
DVV_1_NC_001477.1	0	100.0	70.1	73.0	67.8	60.5	60.4	60.5	60.7	55.8	60.6	60.3	60.6	58.0	57.9	57.9	58.0	62.3	62.3	61.3	
DVV_16681_NC_001474.2	1	70.1	100.0	70.8	68.6	60.5	60.5	60.6	60.7	54.9	60.9	60.3	60.4	58.3	58.3	58.3	58.3	62.7	62.8	62.8	
DVV_3_NC_001475.2	2	73.0	70.8	100.0	68.9	60.2	60.1	60.1	60.1	55.8	60.3	60.0	60.1	57.5	57.6	57.5	57.5	62.6	62.7	62.7	
DVV_4_NC_002640.1	3	67.8	68.6	68.9	100.0	60.5	60.6	60.6	60.4	55.4	60.8	60.3	60.5	58.0	57.9	57.9	57.9	62.1	62.0	62.0	
JEV_SA14-14-2_AF315119.1	4	60.5	60.5	60.2	60.5	100.0	99.8	99.4	99.5	98.1	56.5	70.6	70.3	57.9	58.0	58.0	58.0	61.9	61.8	61.8	
JEV_SA14-14-2_D90195.1	5	60.4	60.5	60.1	60.6	99.8	100.0	99.4	99.5	98.2	56.6	70.6	70.4	57.9	58.0	57.9	58.0	61.9	61.8	61.8	
JEV_SA14-D90194.1	6	60.5	60.5	60.1	60.6	99.4	99.4	100.0	99.8	98.6	56.6	70.8	70.5	58.0	58.0	58.0	58.0	61.9	61.8	61.8	
JEV_virus_M55509.1	7	60.5	60.6	60.1	60.6	99.5	99.5	99.8	100.0	98.6	56.7	70.9	70.4	58.0	58.1	58.0	58.1	61.9	61.8	61.8	
JEV_virus_NC_001437.1	8	60.7	60.7	60.1	60.4	98.1	98.2	98.5	98.6	100.0	56.6	70.6	70.5	58.3	58.3	58.4	58.3	62.1	62.0	62.0	
TEV_virus_NC_001672.1	9	55.8	54.9	55.8	55.4	56.5	56.6	56.6	56.7	56.6	100.0	56.2	56.7	56.6	57.0	57.0	57.0	56.6	56.7	56.7	
WNV_956_NC_001563.2	10	60.6	60.9	60.3	60.8	70.6	70.6	70.8	70.8	70.6	56.2	100.0	79.6	58.1	58.0	58.1	58.2	62.4	62.3	62.3	
WNV_Chin-01_AY490240.2	11	60.3	60.3	60.0	60.3	70.3	70.4	70.5	70.4	70.5	56.7	79.6	100.0	95.3	58.2	58.2	58.2	62.0	62.1	62.1	
WNV_NY99_isol-385-99_NC_009942.1	12	60.6	60.4	60.1	60.5	70.3	70.3	70.4	70.3	70.6	56.6	79.6	95.3	100.0	57.8	57.8	57.8	62.0	62.0	62.0	
YFV_17D_vaccine_strain_NC_002031.1	13	58.0	58.3	57.5	58.0	57.9	57.9	58.0	58.0	58.3	56.9	58.1	58.2	57.8	100.0	99.4	99.9	58.5	58.5	58.5	
YFV_ASIBI_AY640589.1	14	57.9	58.3	57.6	57.9	58.0	58.0	58.1	58.3	57.0	58.0	58.0	58.2	57.8	99.4	100.0	99.4	58.4	58.4	58.1	
YFV_Pasteur_17D-204_XI5062.1	15	57.9	58.3	57.5	57.9	58.0	57.9	58.0	58.4	57.0	58.1	58.2	57.8	99.9	99.4	100.0	99.9	58.4	58.4	58.4	
YFV_vaccine_strain_17D-213_U17067.1	16	58.0	58.3	57.5	57.9	58.0	58.0	58.1	58.3	57.0	58.2	58.2	57.8	99.9	99.4	99.9	100.0	58.4	58.4	58.4	
ZWV_MR766-111D_LC002520.1	17	62.3	62.7	62.6	62.1	61.8	61.9	61.9	62.1	56.6	62.4	62.0	62.0	58.5	58.4	58.4	58.4	100.0	99.7	99.7	
ZWV_MR_766_AY632535.2	18	62.3	62.8	62.7	62.0	61.8	61.8	61.8	62.0	56.7	62.3	62.1	62.0	58.5	58.4	58.4	58.4	99.7	100.0	100.0	
ZWV_MR_766_NC_012532.1	19	62.3	62.8	62.7	62.0	61.8	61.8	61.8	61.8	56.7	62.3	62.1	62.0	58.5	58.4	58.4	58.4	99.7	100.0	100.0	
ZWV_ZikaSPH2015_KU321639.1	20	61.3	62.2	62.5	62.1	61.4	61.5	61.6	61.7	56.7	62.2	62.7	62.4	58.2	58.1	58.2	58.1	88.9	88.8	88.8	

60 % Identity and higher
70 % Identity and higher
80 % Identity and higher

Figure 4

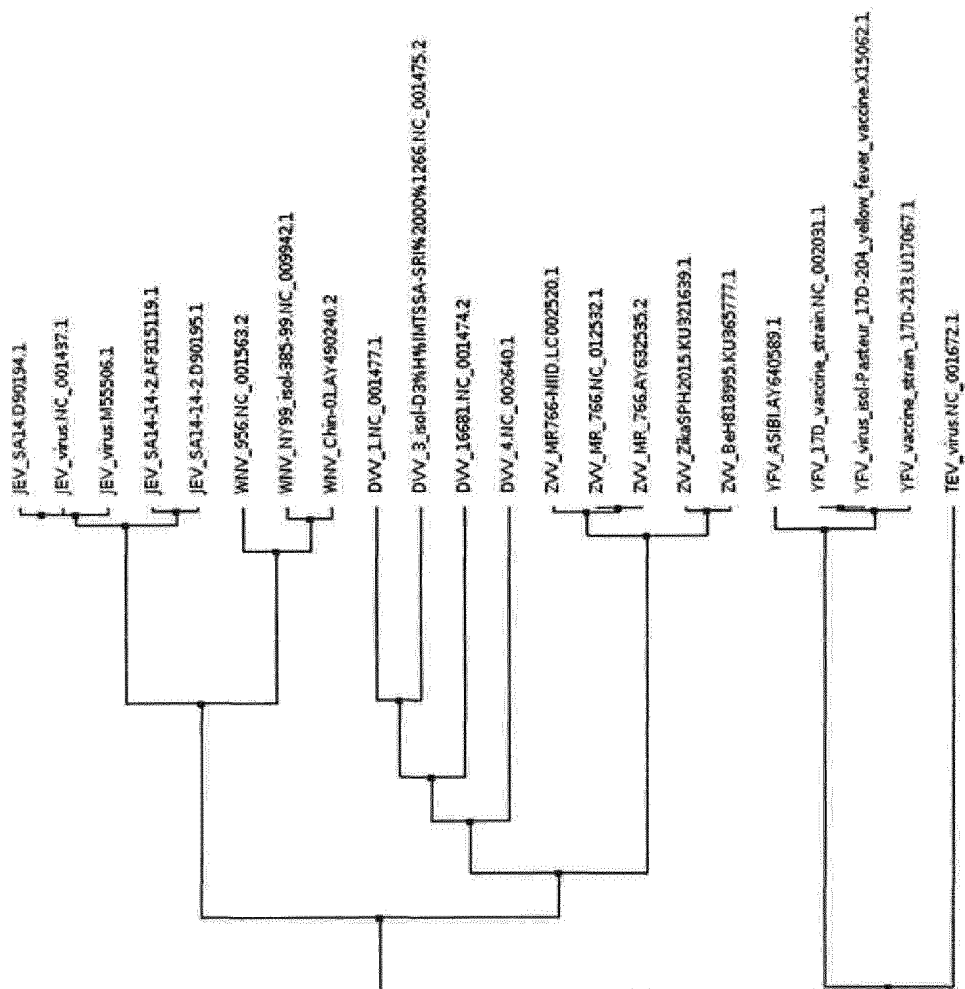


Figure 5

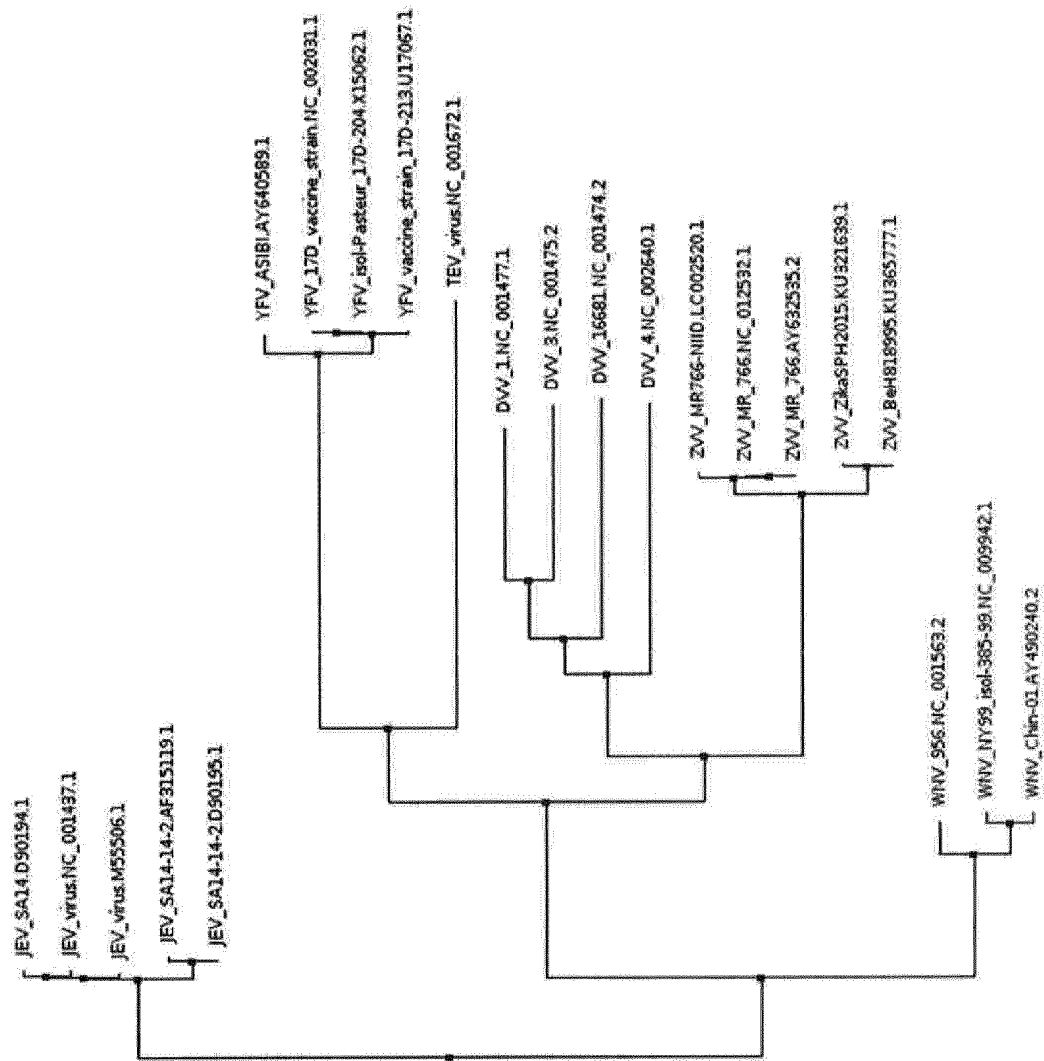


Figure 6

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
DVV_1_NC_001477.1	0	100.0	68.7	77.4	63.8	49.7	49.7	50.1	49.9	50.5	38.3	51.5	50.5	50.9	43.0	43.8	43.0	43.2	57.3	57.9	58.4	58.4	57.1
DVV_16681_NC_001474.2	1	68.7	100.0	68.7	64.0	46.7	46.7	47.1	46.9	47.5	38.9	48.4	47.6	47.6	43.6	44.4	43.6	43.6	53.6	53.8	54.2	54.2	53.8
DVV_3_NC_001475.2	2	77.4	68.7	100.0	62.8	48.0	48.0	48.2	48.2	48.6	38.2	46.8	46.7	46.3	41.6	42.2	41.6	41.7	57.3	57.7	58.2	58.2	57.1
DVV_4_NC_002640.1	3	63.8	64.0	62.8	100.0	47.5	47.5	47.7	47.5	48.1	39.7	49.6	49.6	49.8	40.0	40.6	40.0	40.0	55.8	56.4	56.4	56.4	55.8
JEV_SAI4-14-2_AF315119.1	4	49.7	46.7	48.0	47.5	100.0	98.8	98.0	98.6	97.8	39.6	76.1	76.5	76.7	43.1	42.9	43.1	43.1	54.0	54.8	54.8	54.8	54.0
JEV_SAI4-14-2_D90195.1	5	49.7	46.7	48.0	47.5	99.8	100.0	98.2	98.8	98.0	39.8	76.3	76.7	76.9	43.1	42.9	43.1	43.1	54.0	54.8	54.8	54.8	54.0
JEV_SAI4_D90194.1	6	50.1	47.1	48.2	47.7	98.0	98.2	100.0	99.4	99.4	40.0	77.5	77.8	78.0	43.3	43.3	43.3	43.3	54.4	55.4	55.2	55.2	54.4
JEV_virus_M55506.1	7	49.9	46.9	48.2	47.5	98.6	98.8	99.4	100.0	99.2	40.0	77.3	77.6	77.8	43.3	43.3	43.3	43.3	54.2	55.2	55.0	55.0	54.2
JEV_virus_NC_001437.1	8	50.5	47.5	48.6	48.1	97.8	98.0	99.4	98.2	100.0	40.4	78.0	78.4	78.6	43.5	43.5	43.5	43.5	54.8	55.4	55.2	55.2	54.8
TEV_virus_NC_001672.1	9	38.3	38.9	38.2	39.7	39.6	39.8	40.0	40.0	40.4	100.0	41.3	41.6	41.0	42.3	41.9	42.3	42.3	39.9	39.9	39.6	39.6	39.9
WNV_956_NC_001563.2	10	51.5	48.4	46.8	49.6	76.1	76.3	77.5	77.3	78.0	41.3	100.0	94.8	94.0	43.8	43.6	43.8	43.8	55.0	55.0	54.8	54.8	55.0
WNV_Chin-01_AY490240.2	11	50.5	47.6	46.7	49.6	76.5	76.7	77.8	77.6	78.4	41.6	94.8	100.0	98.8	43.9	43.5	43.9	43.9	54.4	54.2	54.0	54.0	54.4
WNV_NY99_isol-385-99_NC_009942.1	12	50.9	47.6	46.3	49.8	76.7	76.9	78.0	77.8	78.6	41.0	94.0	98.8	100.0	43.9	43.5	43.9	43.9	54.0	53.8	53.8	53.8	54.0
YFV_17D_vaccine_strain_NC_002031.1	13	43.0	43.6	41.6	40.0	43.1	43.1	43.3	43.3	43.5	42.3	43.8	43.9	43.9	100.0	97.6	100.0	99.8	42.0	43.4	43.5	43.5	42.0
YFV_ASIBIAY640589.1	14	43.8	44.4	42.2	40.6	42.9	42.9	43.3	43.3	43.5	41.9	43.6	43.5	43.5	97.6	100.0	97.6	97.4	42.4	43.8	43.9	43.9	42.4
YFV_isol-Pasteur_17D-204_X15062.1	15	43.0	43.6	41.6	40.0	43.1	43.1	43.3	43.3	43.5	42.3	43.8	43.9	43.9	100.0	97.6	100.0	99.8	42.0	43.4	43.5	43.5	42.0
YFV_vaccine_strain_17D-213_U17067.1	16	43.2	43.6	41.7	40.0	43.1	43.1	43.3	43.3	43.5	42.3	43.8	43.9	43.9	99.6	97.4	99.8	100.0	42.0	43.4	43.5	43.5	42.0
ZVW_Beh018995_KU365777.1	17	57.3	53.6	57.3	55.8	54.0	54.0	54.4	54.2	54.8	39.9	55.0	54.4	54.0	42.0	42.4	42.0	42.0	96.8	96.4	96.4	96.4	96.8
ZVW_MR766_NHID_LC002520.1	18	57.9	53.8	57.7	56.4	54.8	54.8	55.4	55.2	55.4	39.9	55.0	54.2	53.8	43.4	43.8	43.4	43.4	96.8	100.0	98.8	98.8	96.6
ZVW_MR_766_AY632535.2	19	58.4	54.2	58.2	56.4	54.8	54.8	55.2	55.0	55.2	39.6	54.8	54.0	53.8	43.5	43.9	43.5	43.5	96.4	98.8	100.0	100.0	96.2
ZVW_MR_766_NC_012532.1	20	58.4	54.2	58.2	56.4	54.8	54.8	55.2	55.0	55.2	39.6	54.8	54.0	53.8	43.5	43.9	43.5	43.5	96.4	98.8	100.0	100.0	96.2
ZVW_ZikaSPH2015_KU321639.1	21	57.1	53.8	57.1	55.8	54.0	54.0	54.4	54.2	54.8	39.9	55.0	54.4	54.0	42.0	42.4	42.0	42.0	98.8	96.6	96.2	96.2	100.0

50	% Identity and higher
60	% Identity and higher
70	% Identity and higher

50 % Identity and higher
60 % Identity and higher
70 % Identity and higher

Figure 7 (a)

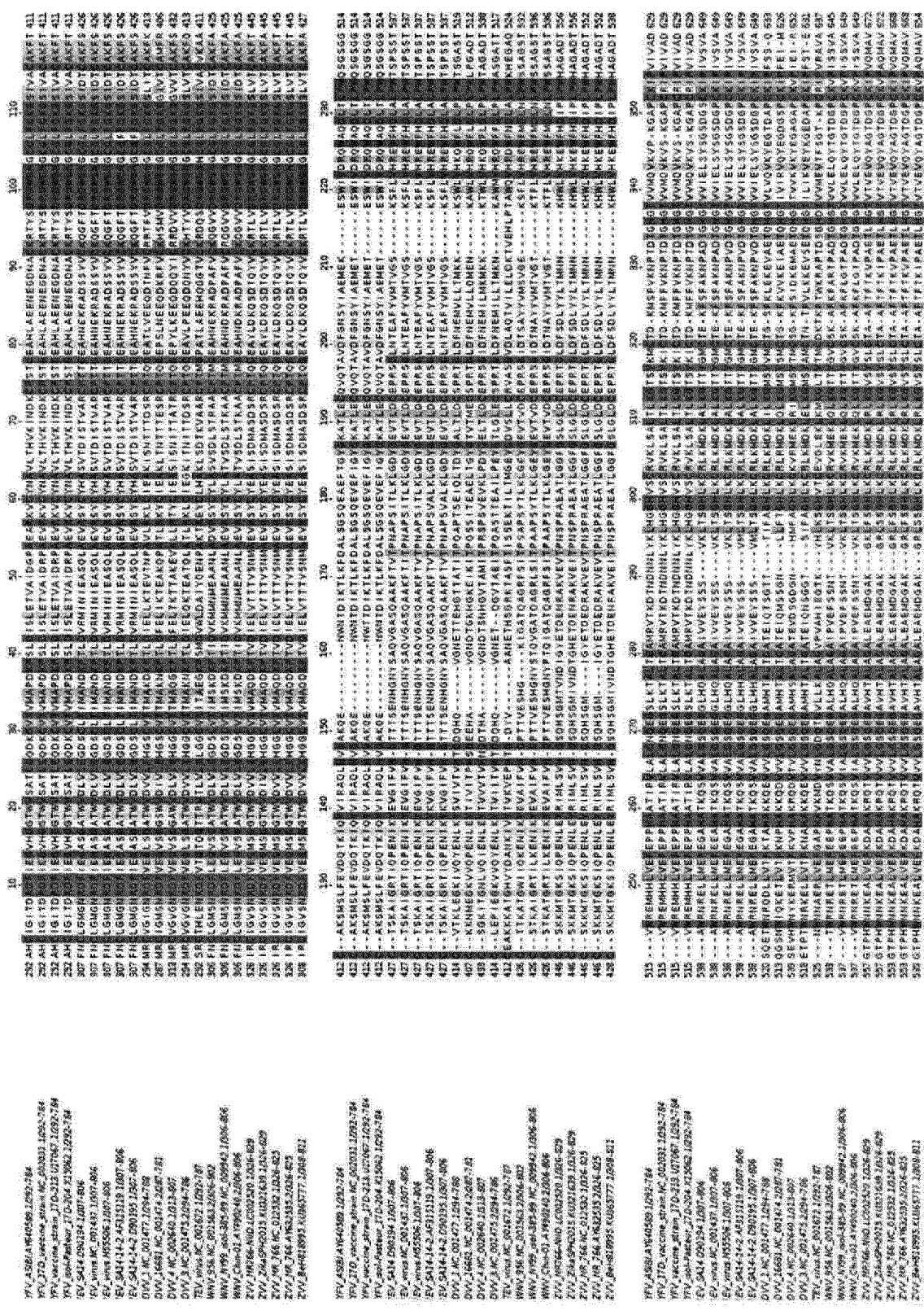


Figure 7 (b)

[illegible][illegible]

Figure 8a

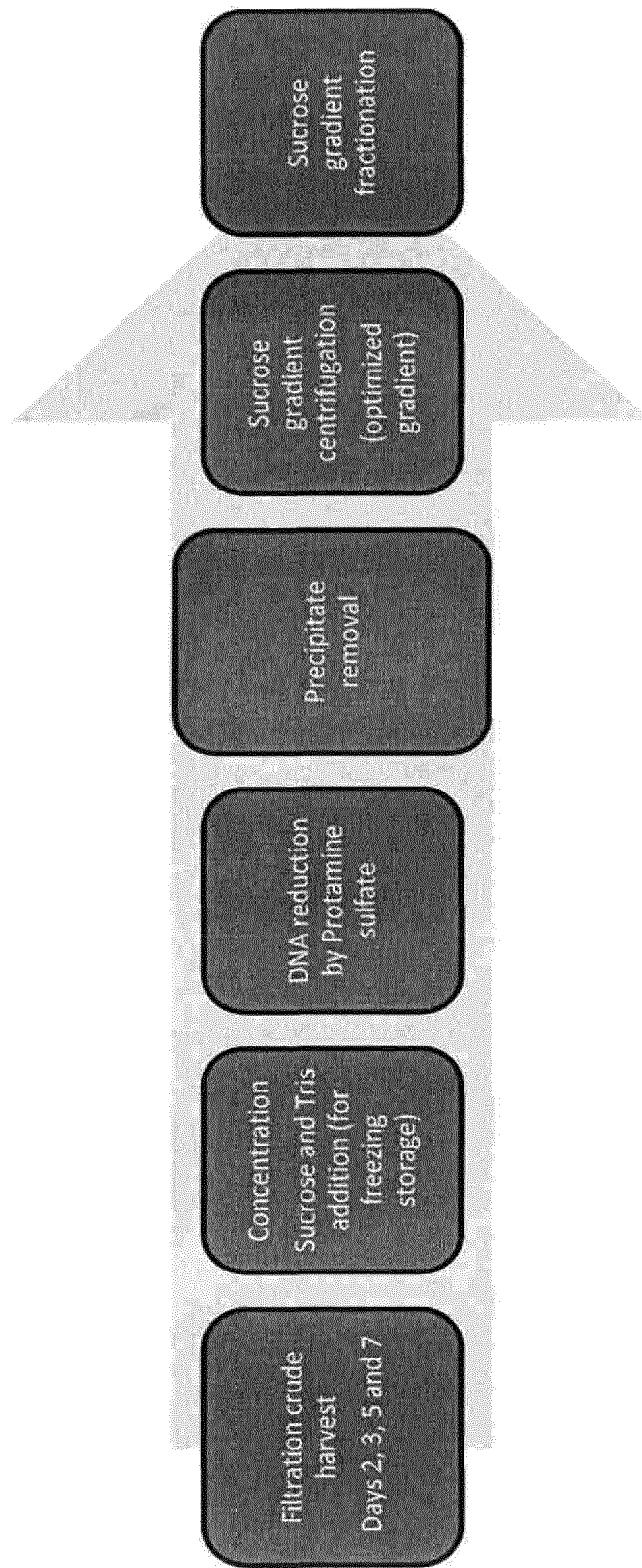


Figure 8b

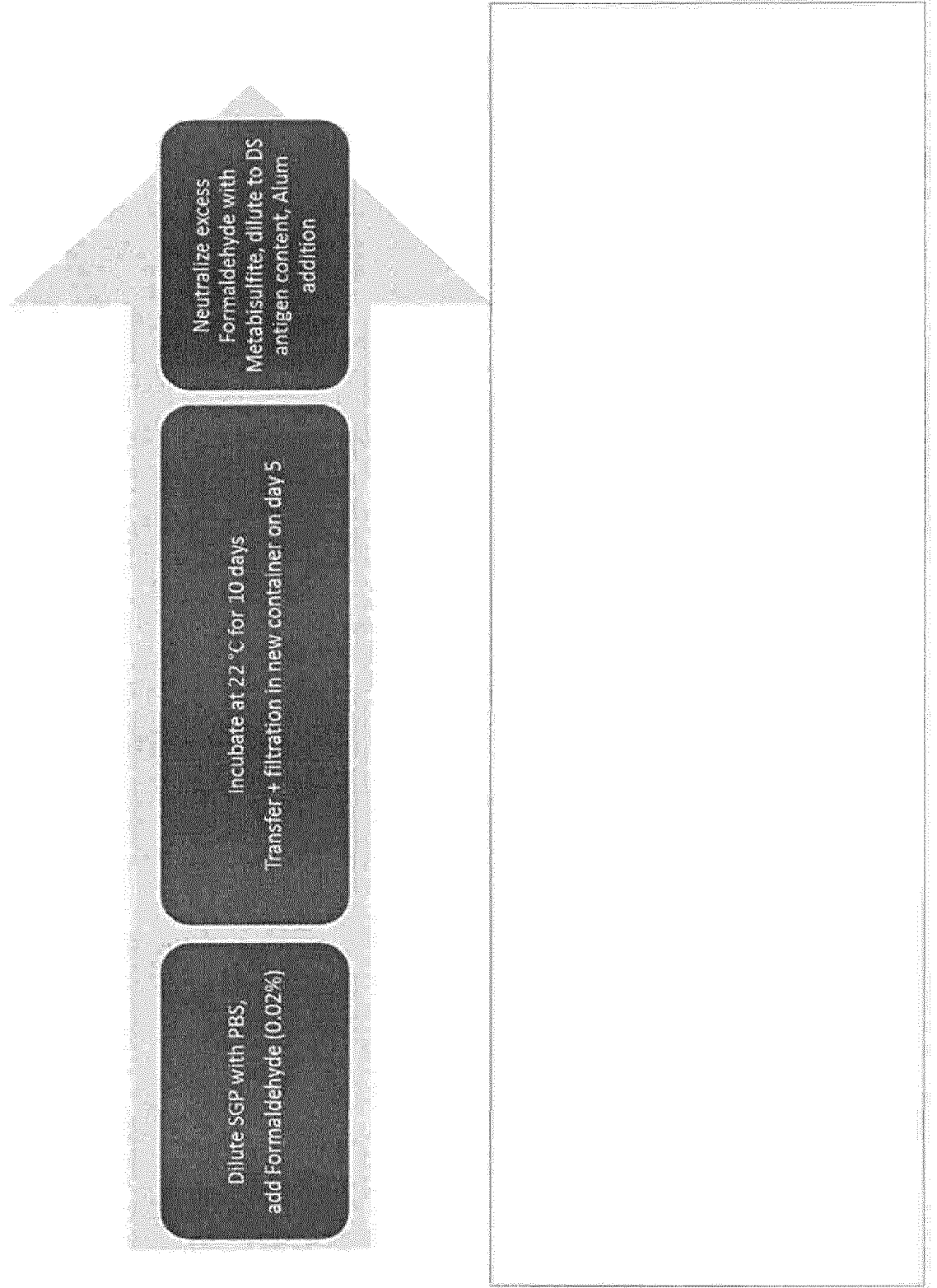
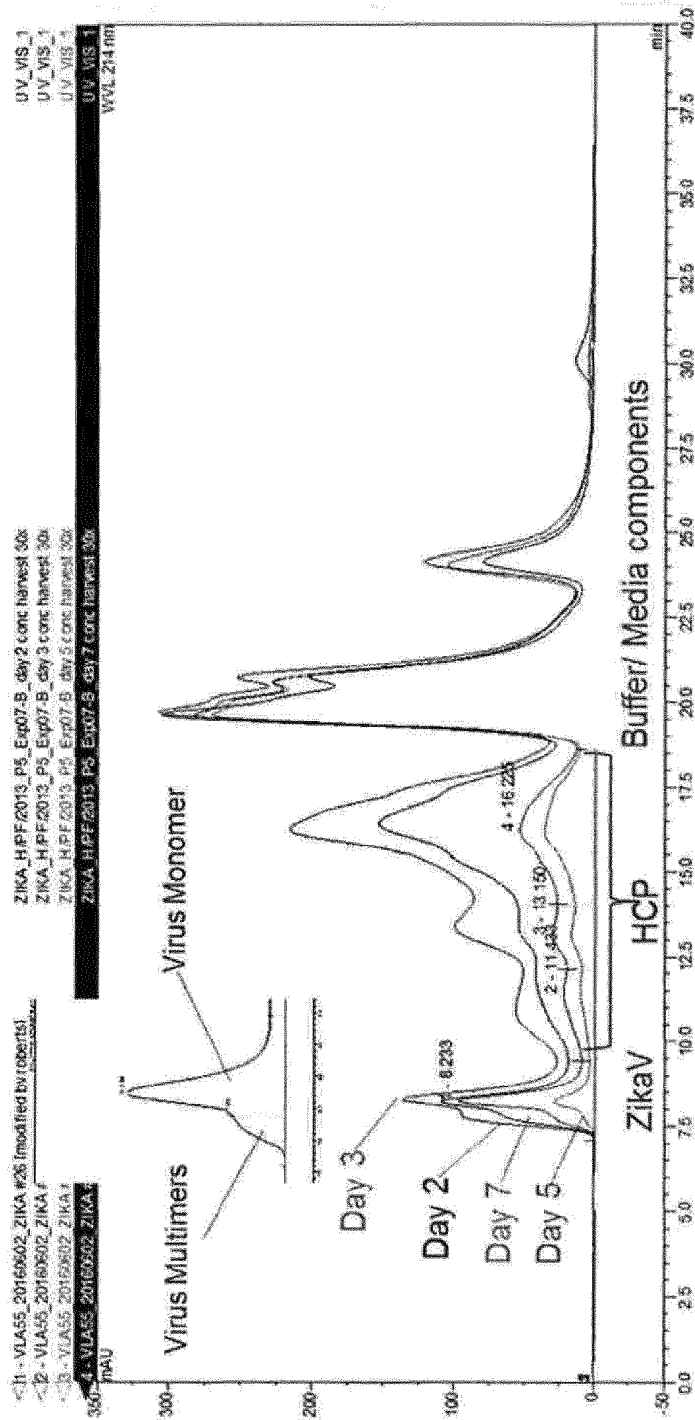
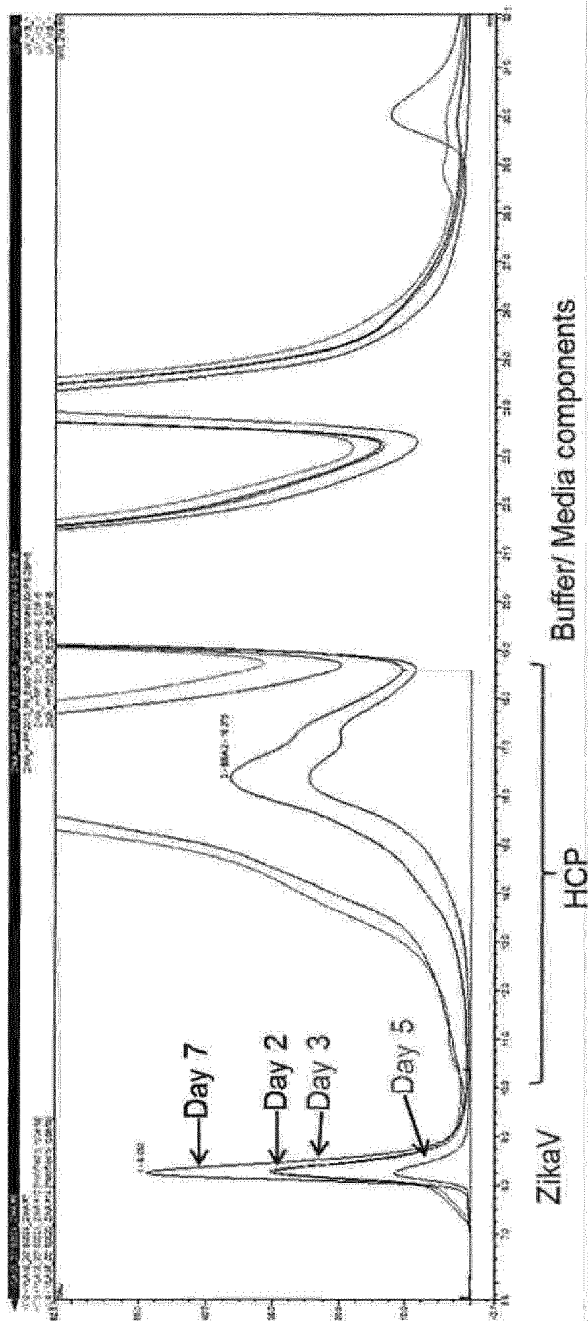
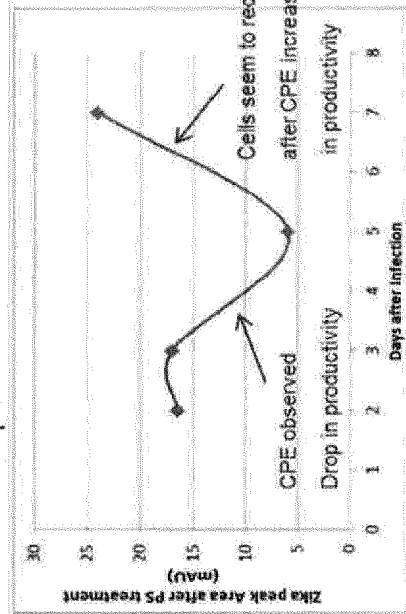


Figure 9



- + Similar virus concentration in harvests Day 2, Day 3, Day 7; lower virus concentration in harvest Day 5
- + Day 2 and Day 3 harvests contain more HCP than Day 5 / 7 (correlates with observed CPE)
- + Minor amount of virus multimers observed

Figure 10



- + Protamine Sulfate removes virus aggregates and partially HCP
- + Infectious virus titer is not affected by PS treatment
- + Strong CPE on day 3, drop in productivity
- + Remaining cells seem to recover well and increase in Zika productivity

Figure 11

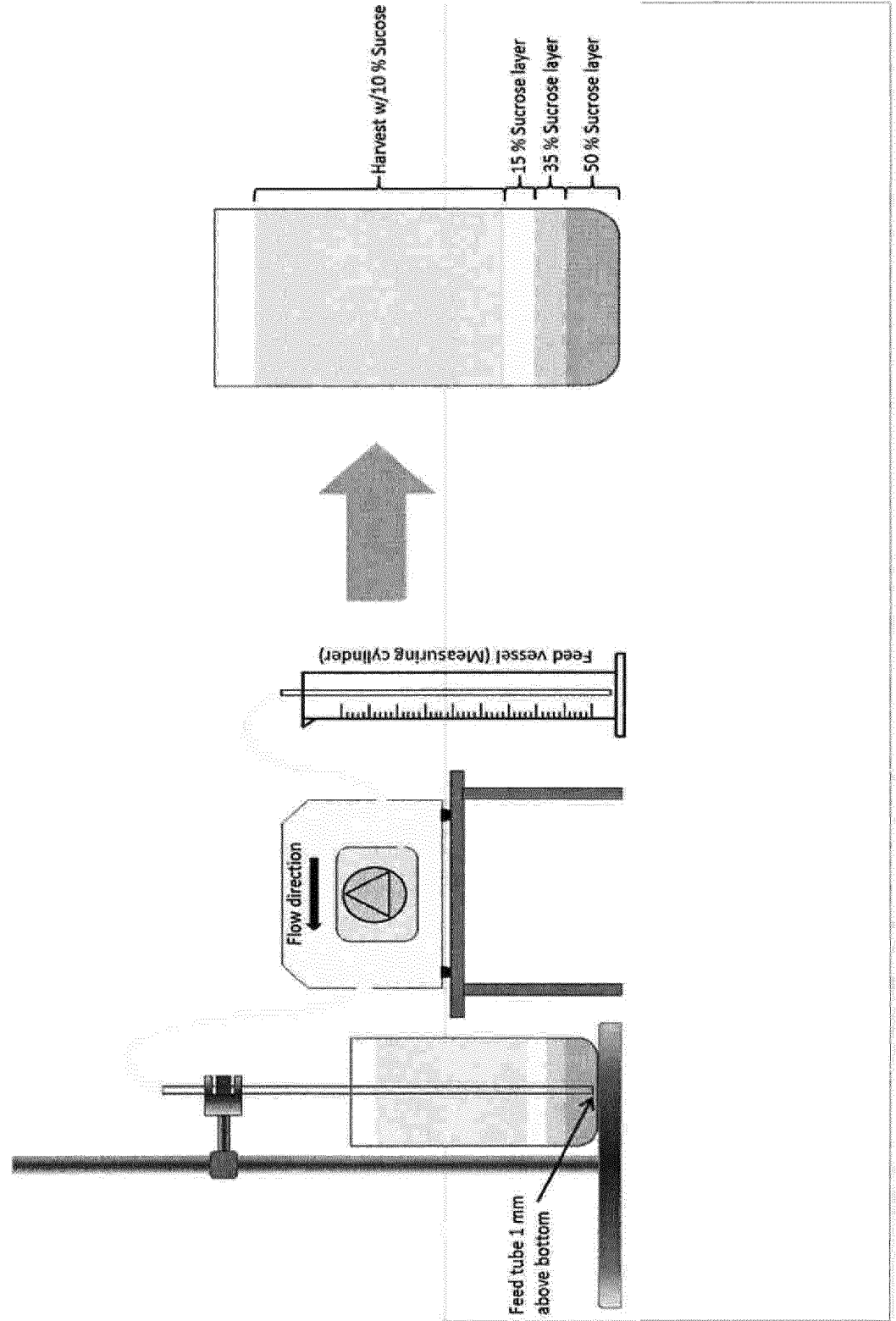
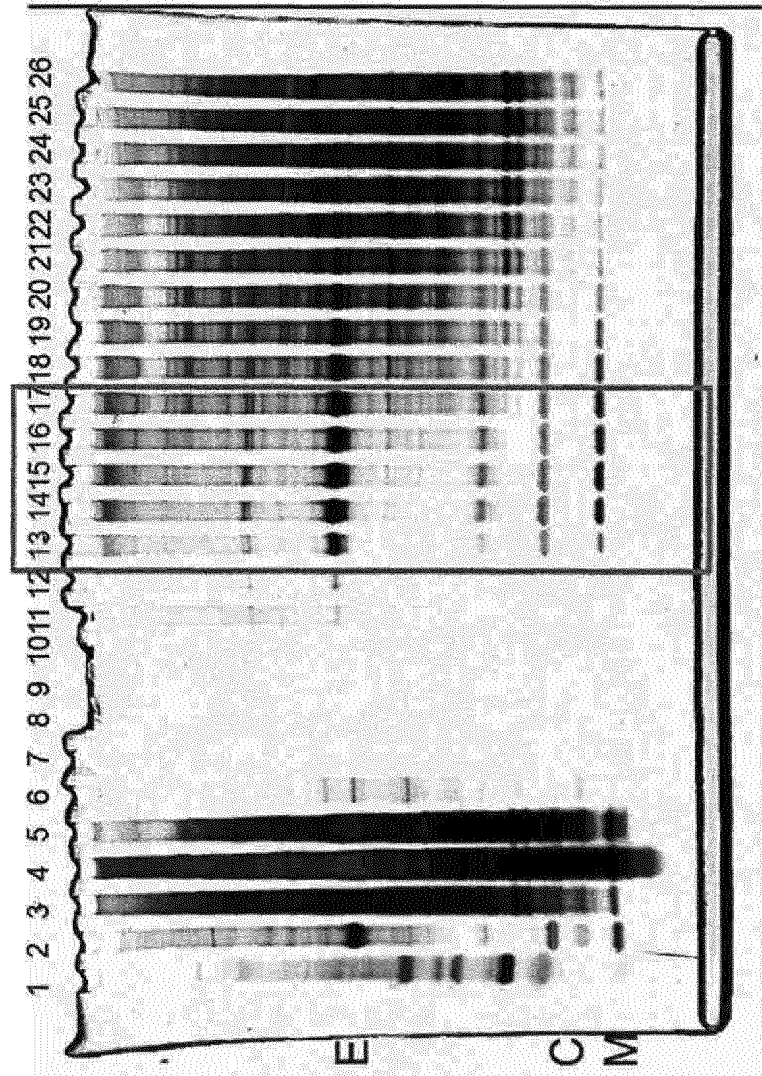


Figure 12



Pooled fractions F10-F14
(10mL total volume per bottle)

Lane	Sample
1	Molecular weight Marker
2	JEV Sucrose Gradient Pool (Reference)
3	Zika Harvest pool (day 2,3,5,7)
4	Zika Harvest pool (day 2,3,5,7) concentrated 300x
5	Zika Harvest pool (day 2,3,5,7) concentrated 300x + Protamine sulfate
6	Ultrafiltration Permeate
7	SGC Bottle 1, Fraction 4
8	SGC Bottle 1, Fraction 5
9	SGC Bottle 1, Fraction 6
10	SGC Bottle 1, Fraction 7
11	SGC Bottle 1, Fraction 8
12	SGC Bottle 1, Fraction 9
13	SGC Bottle 1, Fraction 10
14	SGC Bottle 1, Fraction 11
15	SGC Bottle 1, Fraction 12
16	SGC Bottle 1, Fraction 13
17	SGC Bottle 1, Fraction 14
18	SGC Bottle 1, Fraction 15
19	SGC Bottle 1, Fraction 16
20	SGC Bottle 1, Fraction 17
21	SGC Bottle 1, Fraction 18
22	SGC Bottle 1, Fraction 19
23	SGC Bottle 1, Fraction 20
24	SGC Bottle 1, Fraction 21
25	SGC Bottle 1, Fraction 22
26	SGC Bottle 1, Fraction 23

Figure 13

Baseline separation of Virus and PS/HCP

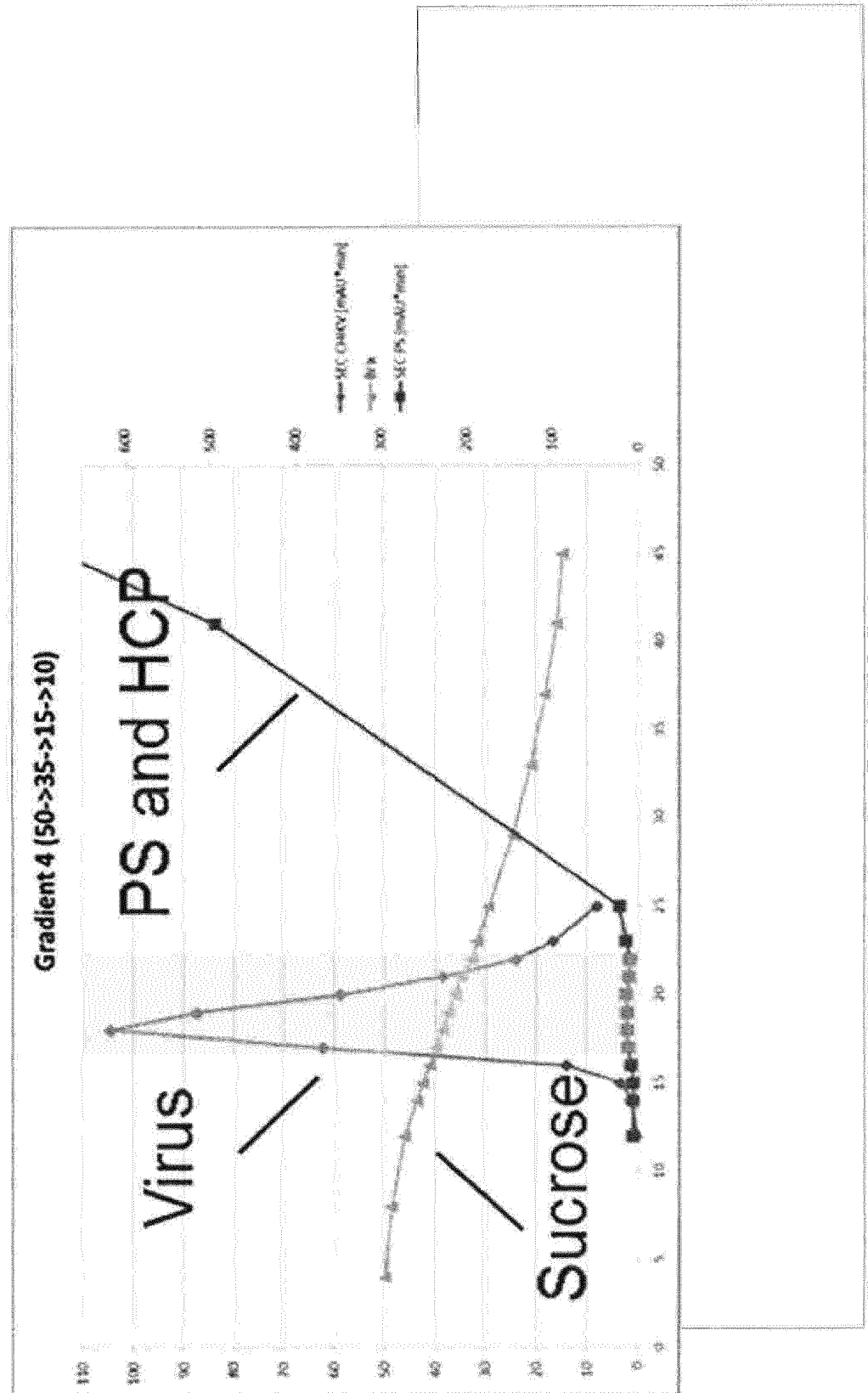


Figure 14

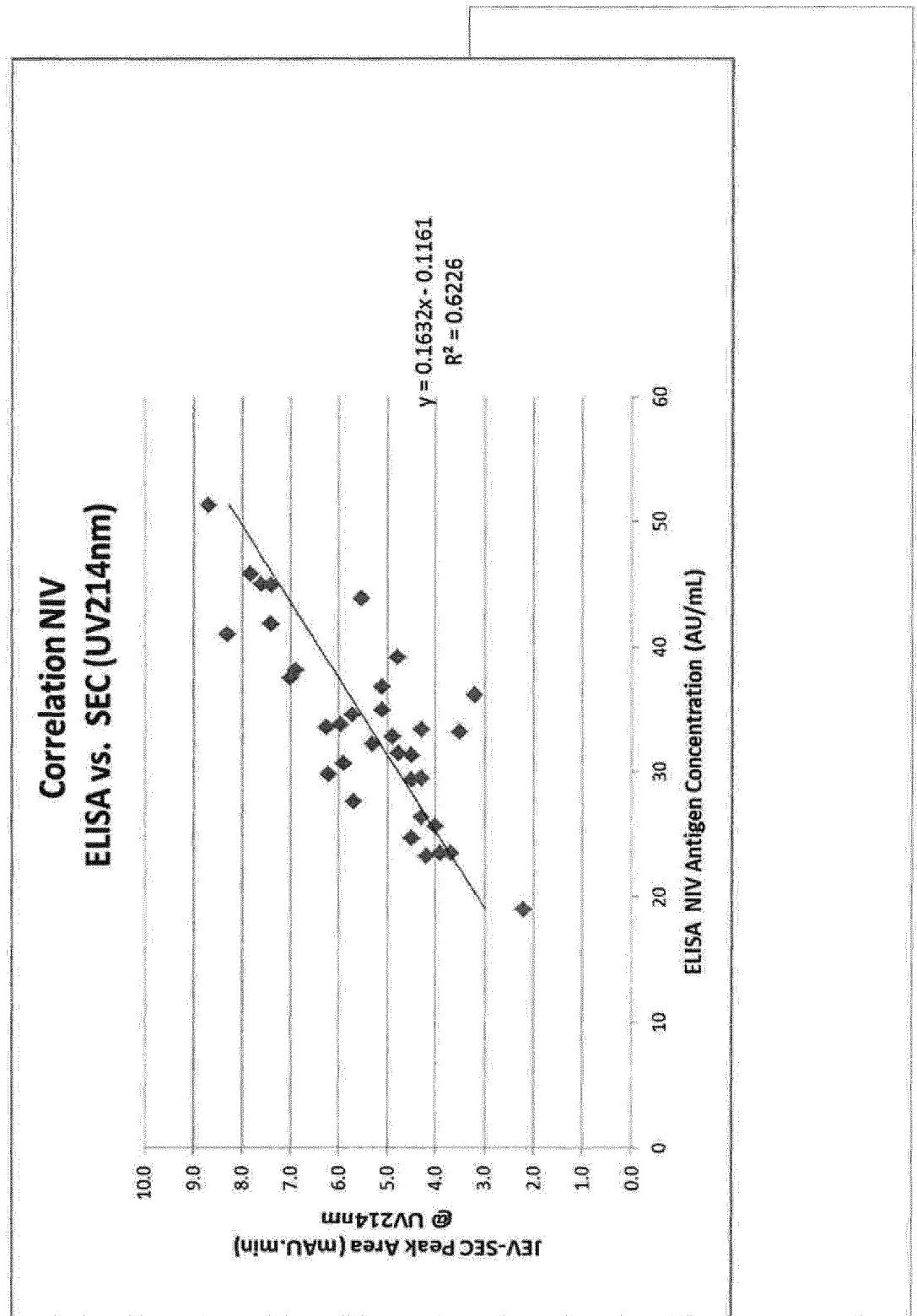
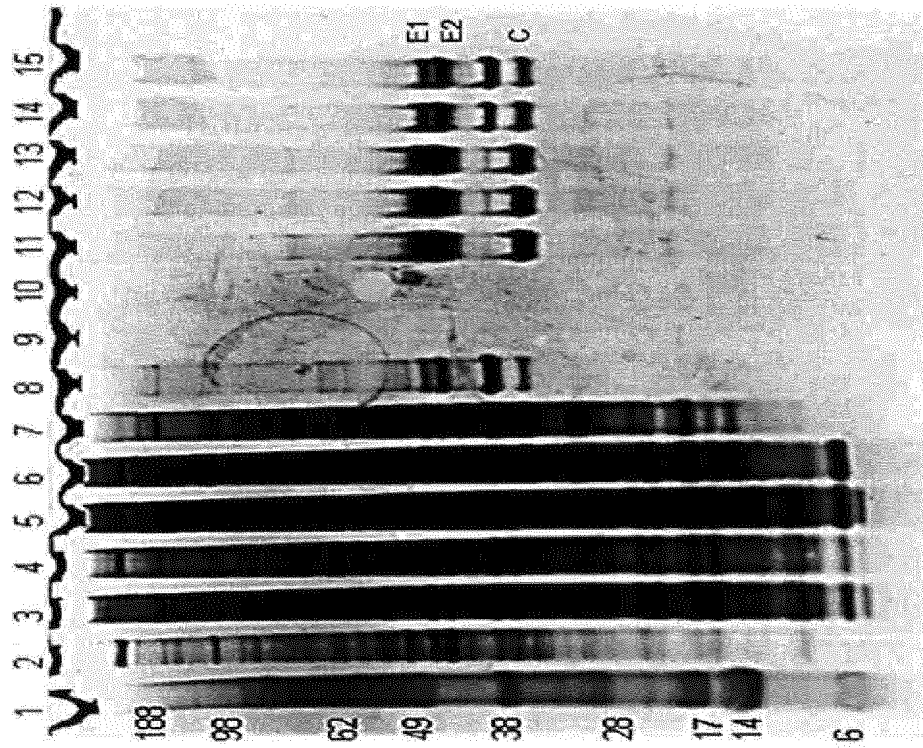


Figure 15



Lane	Sample
1	Marker Seebieplus2
2	CHIKV lot20150812_WVB2015-01_Filtered harvest 0.2µ_24hpi
3	CHIKV lot20150812_WVB2015-01_Filtered harvest 0.2µ_48hpi
4	20150813_CHIKV_DSP_UF/DF_Load
5	20150813_CHIKV_DSP_UF/DF_conc. 10x
6	20150813_CHIKV_DSP_UF/DF_conc.&dia. 11x
7	20150813_CHIKV_DSP_PStreatment
8	20150813_CHIKV_DSP_PS&CC700treatment
9	20150813_CHIKV_DSP_SGCfrac F5
10	20150813_CHIKV_DSP_SGCfrac F6
11	20150813_CHIKV_DSP_SGCPoolF7-F10
12	20150813_CHIKV_DSP_SGCPoolF7-F11 (final pool)
13	20150813_CHIKV_DSP_SGCPoolF7-F12
14	20150813_CHIKV_DSP_SGCfrac F13
15	20150813_CHIKV_DSP_SGCfrac F14

Figure 16a

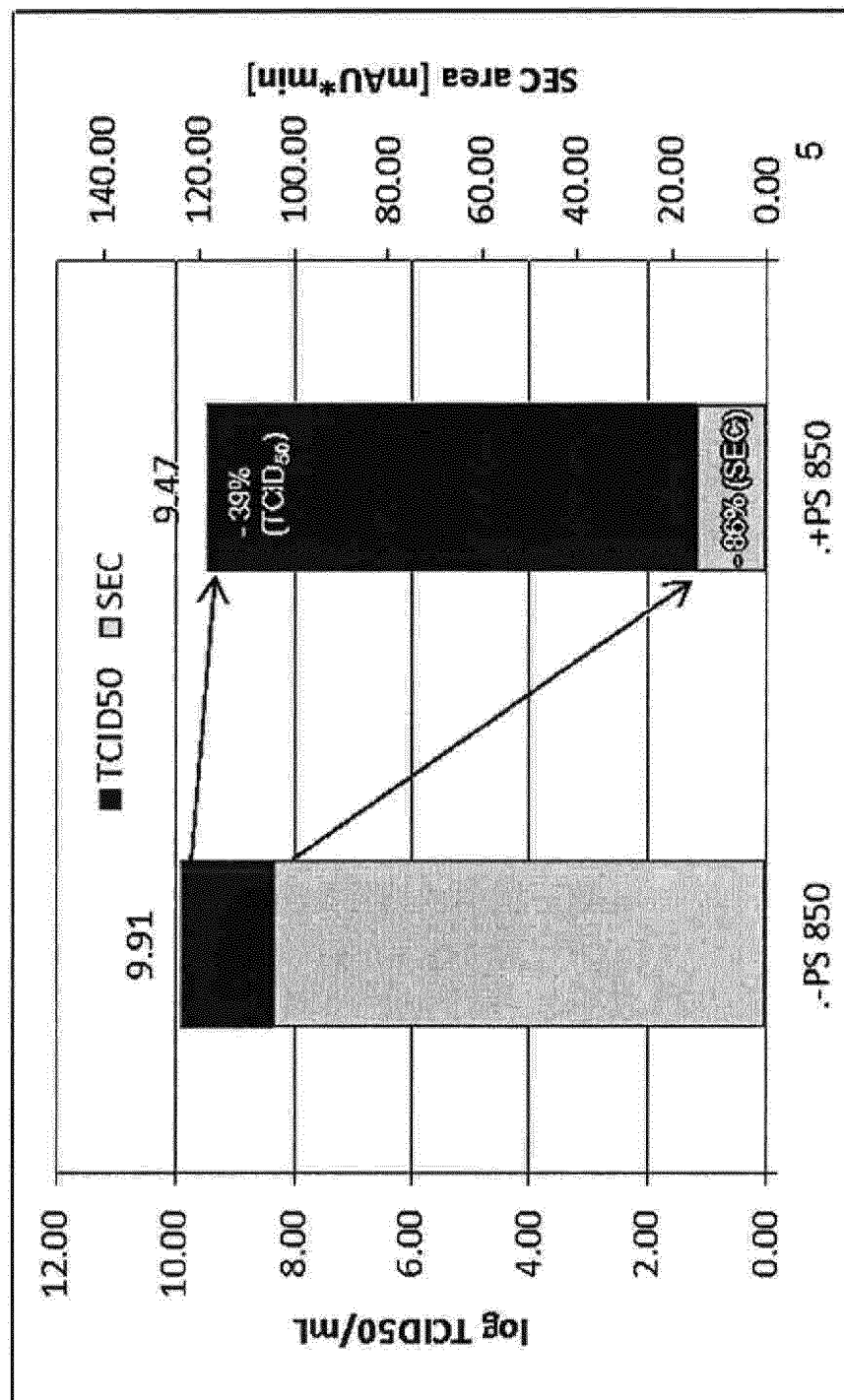


Figure 16b

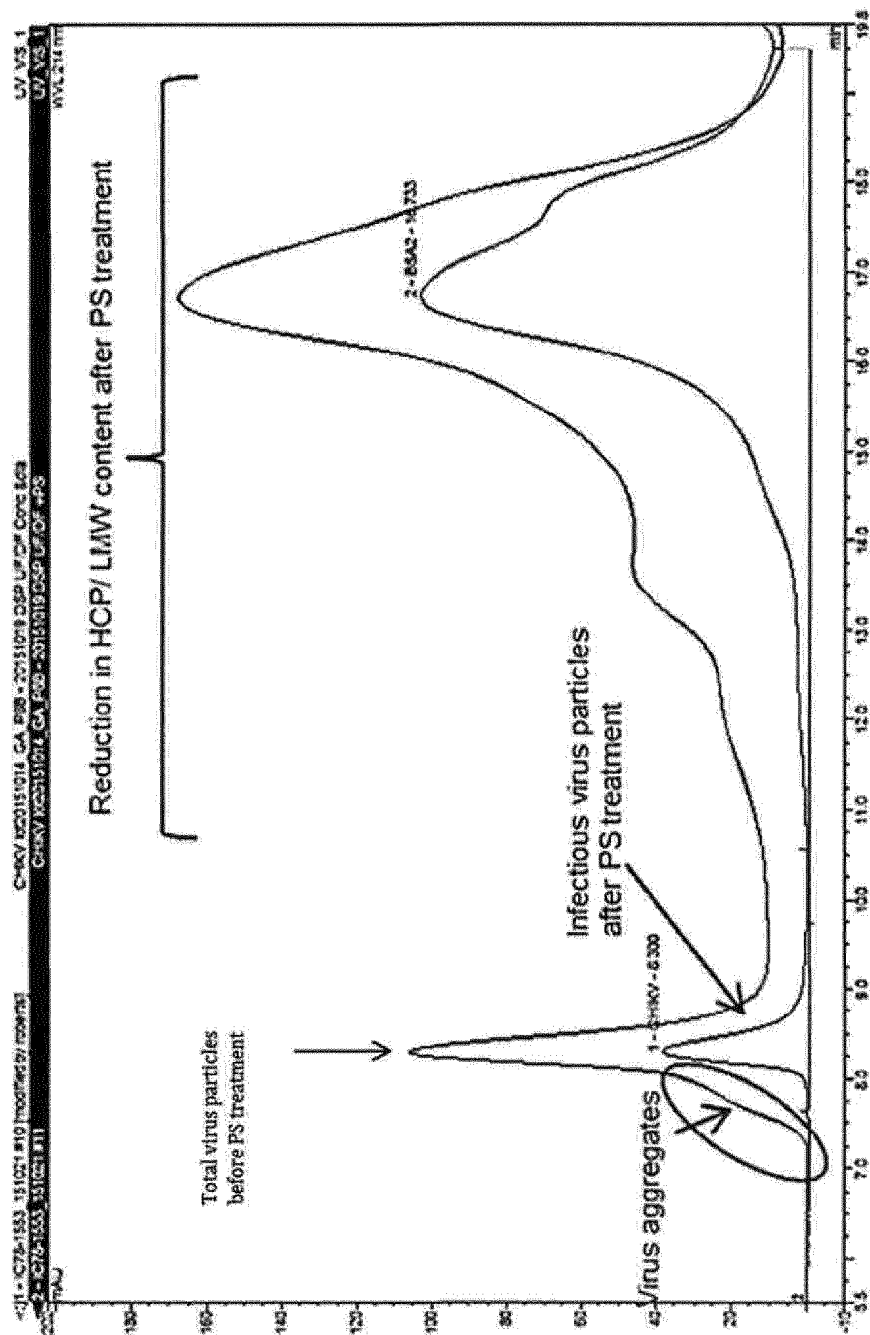


Figure 17

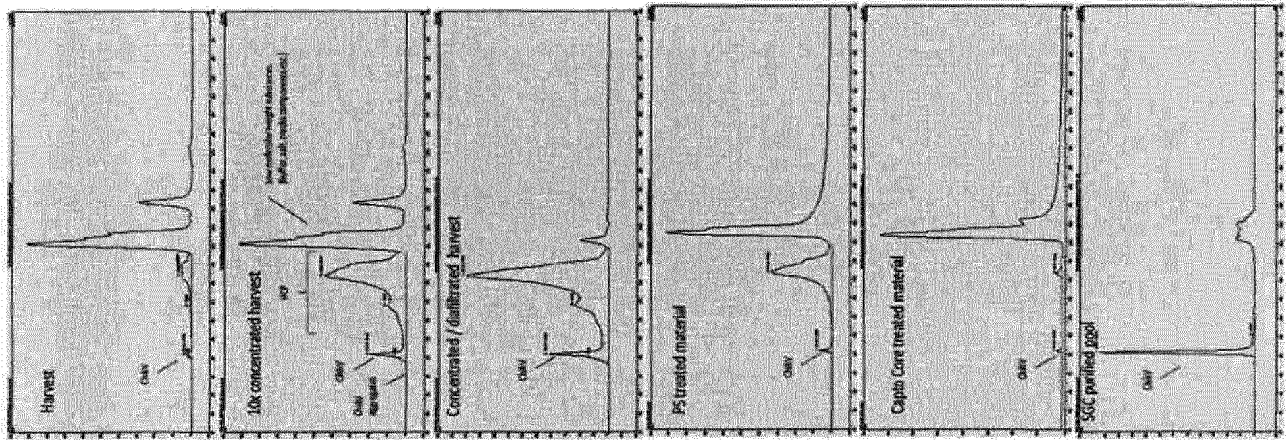


Figure 18a

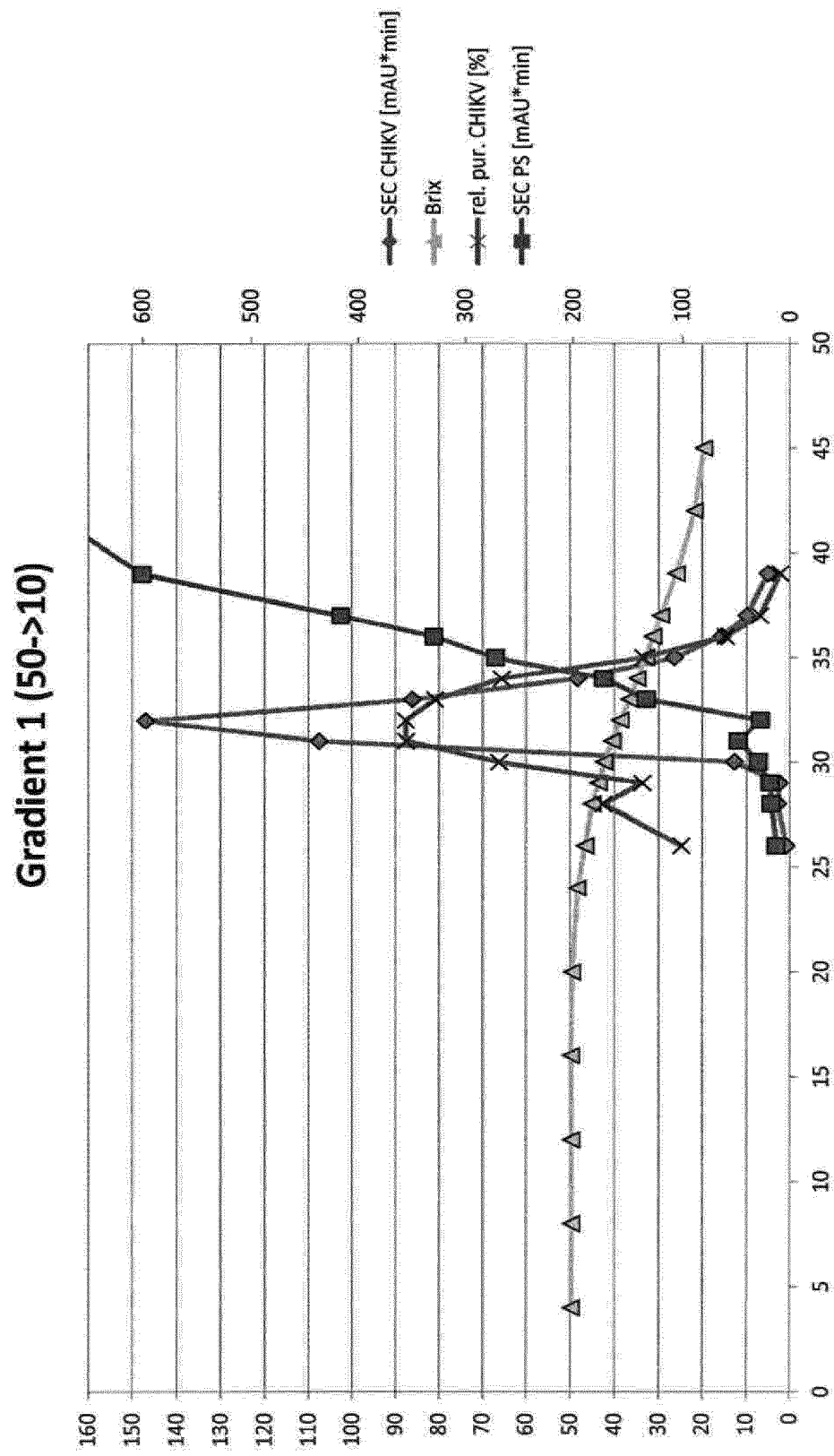


Figure 18b

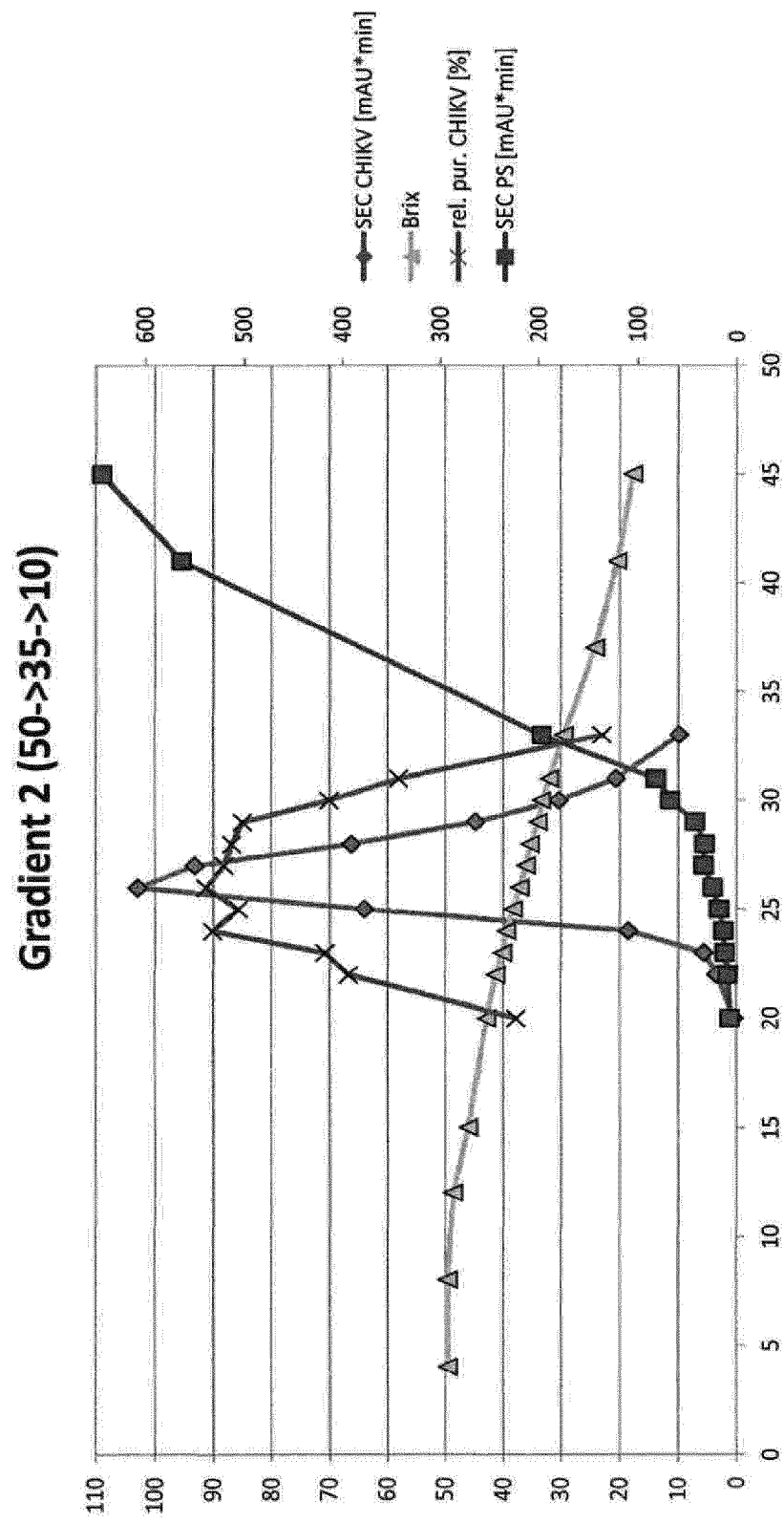


Figure 18c

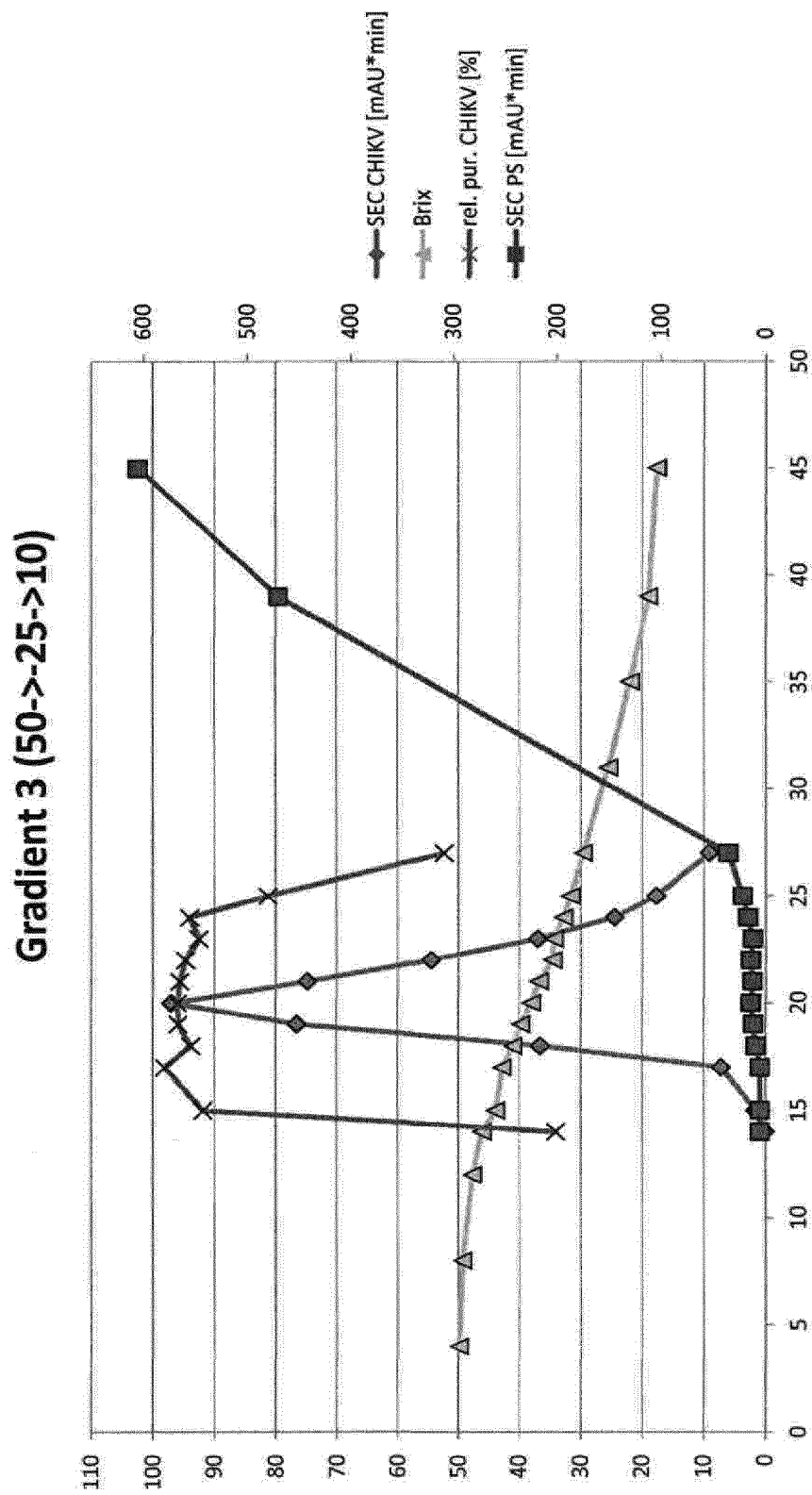


Figure 18d

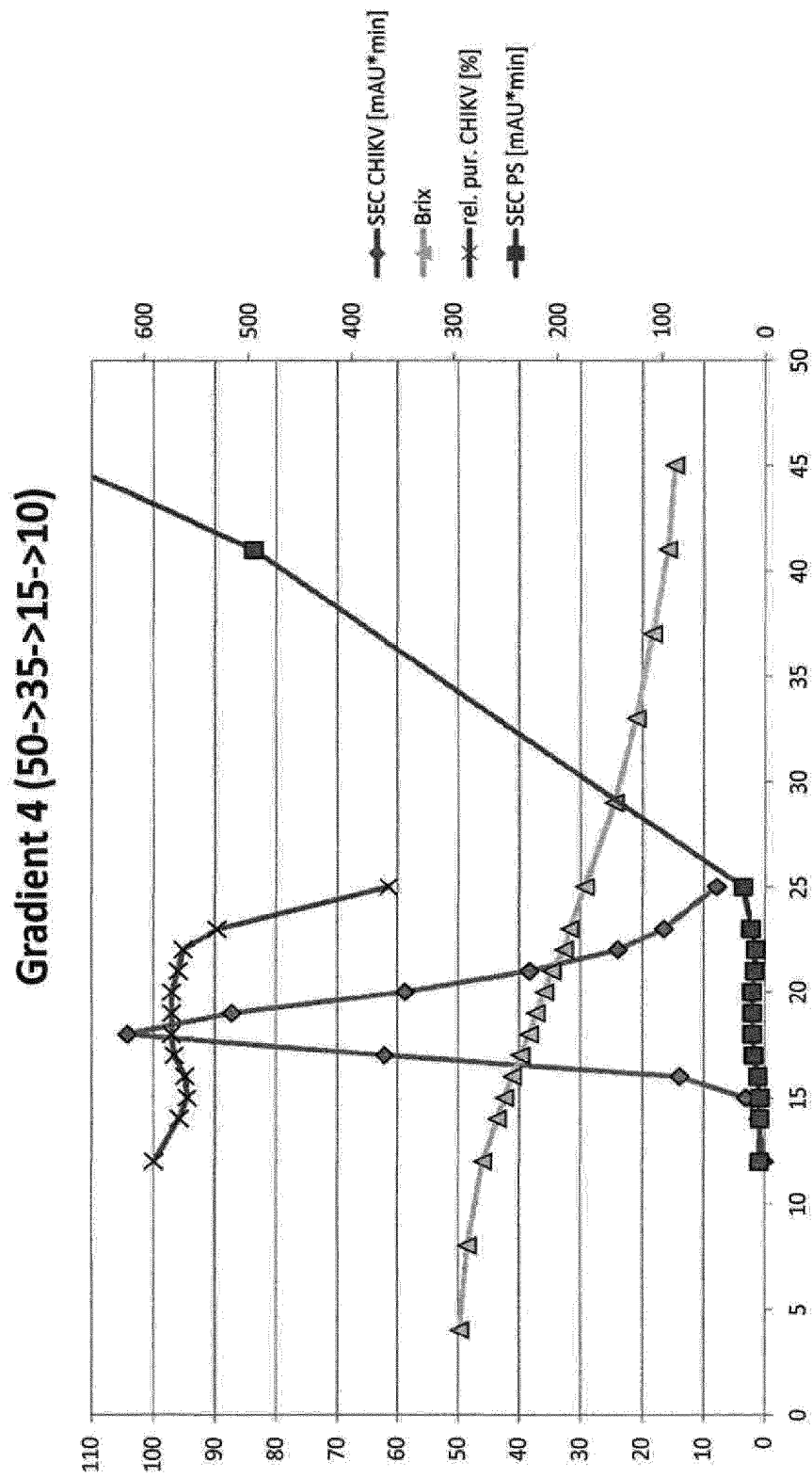


Figure 19

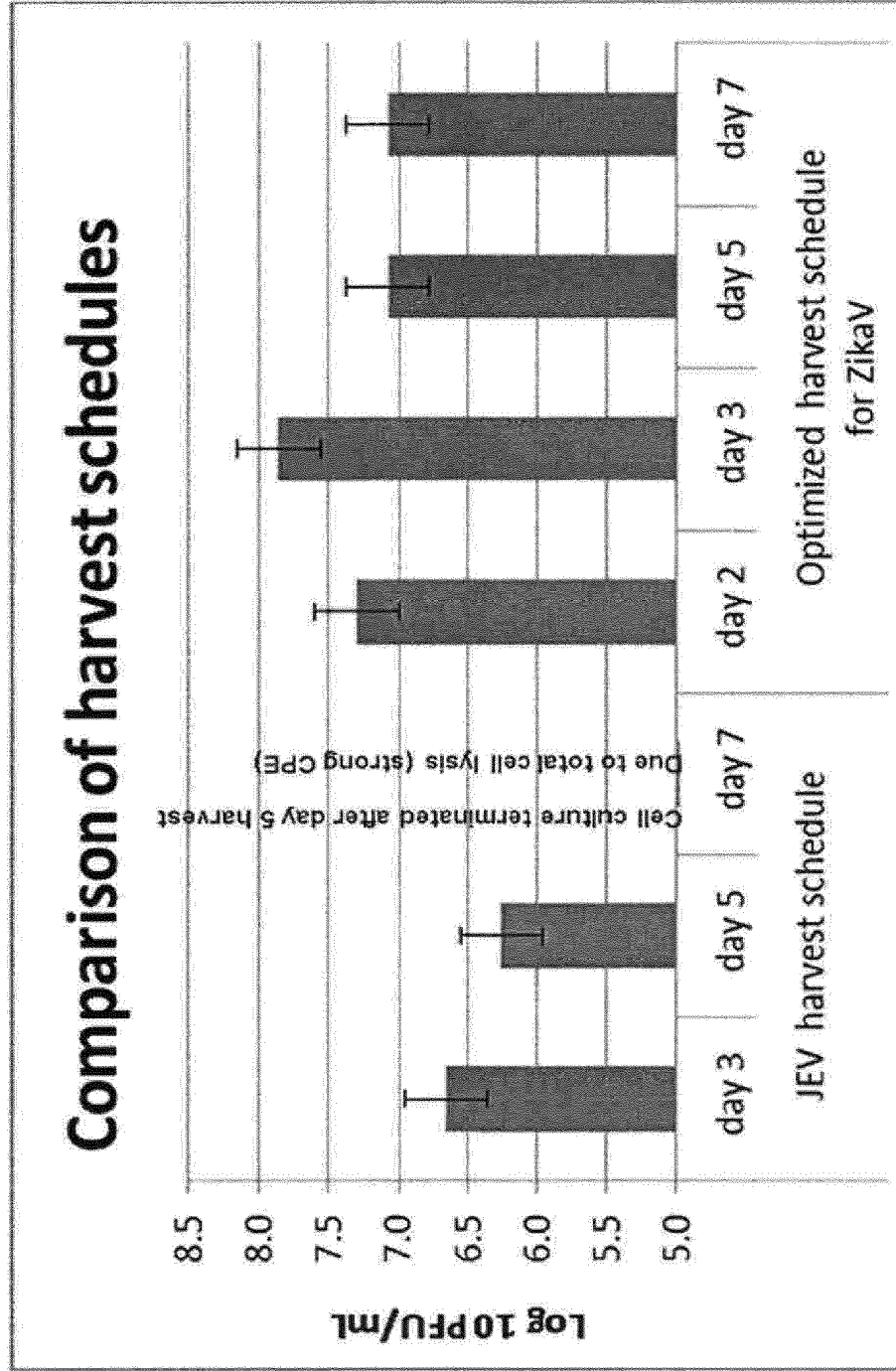


Figure 20

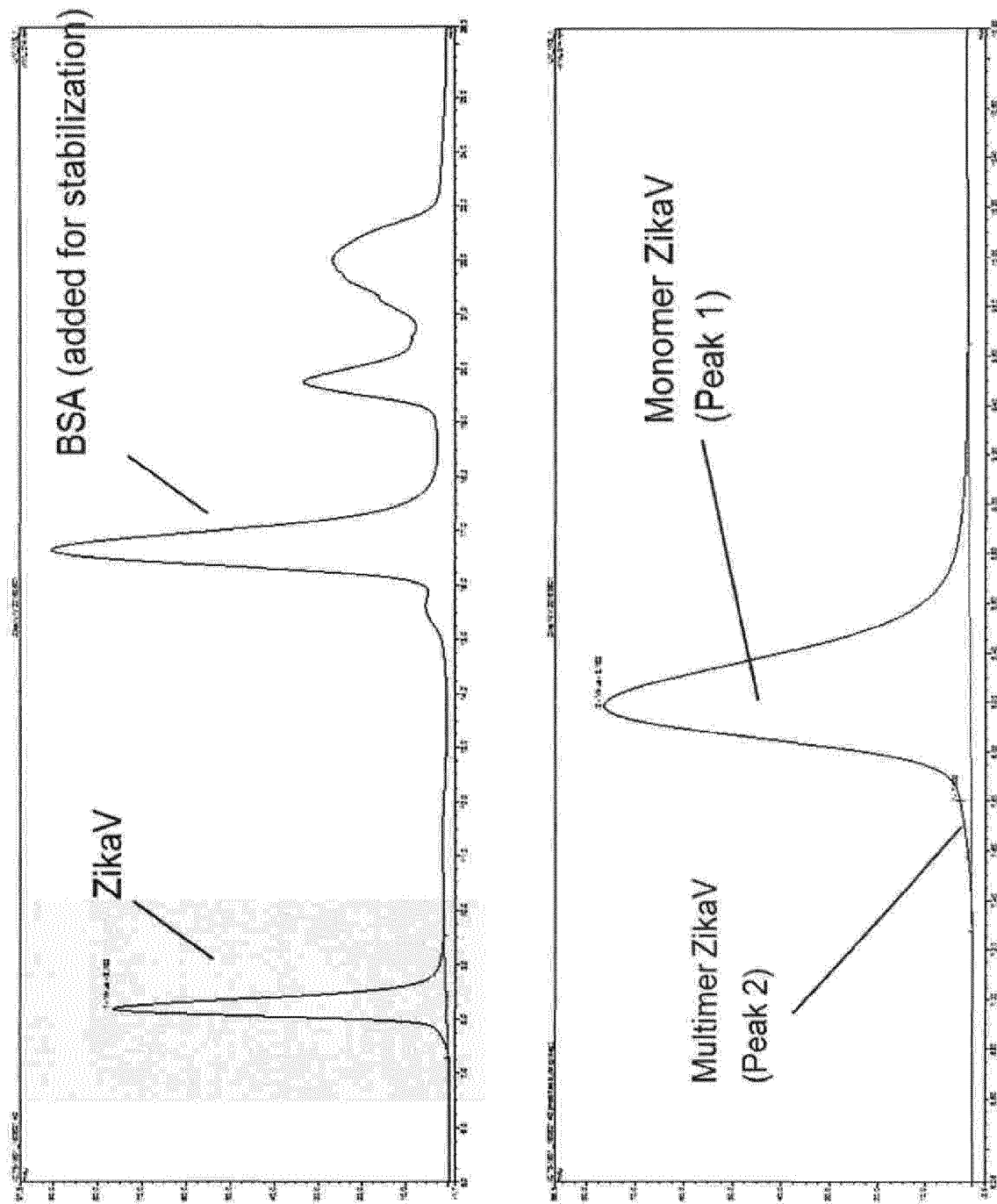


Figure 21

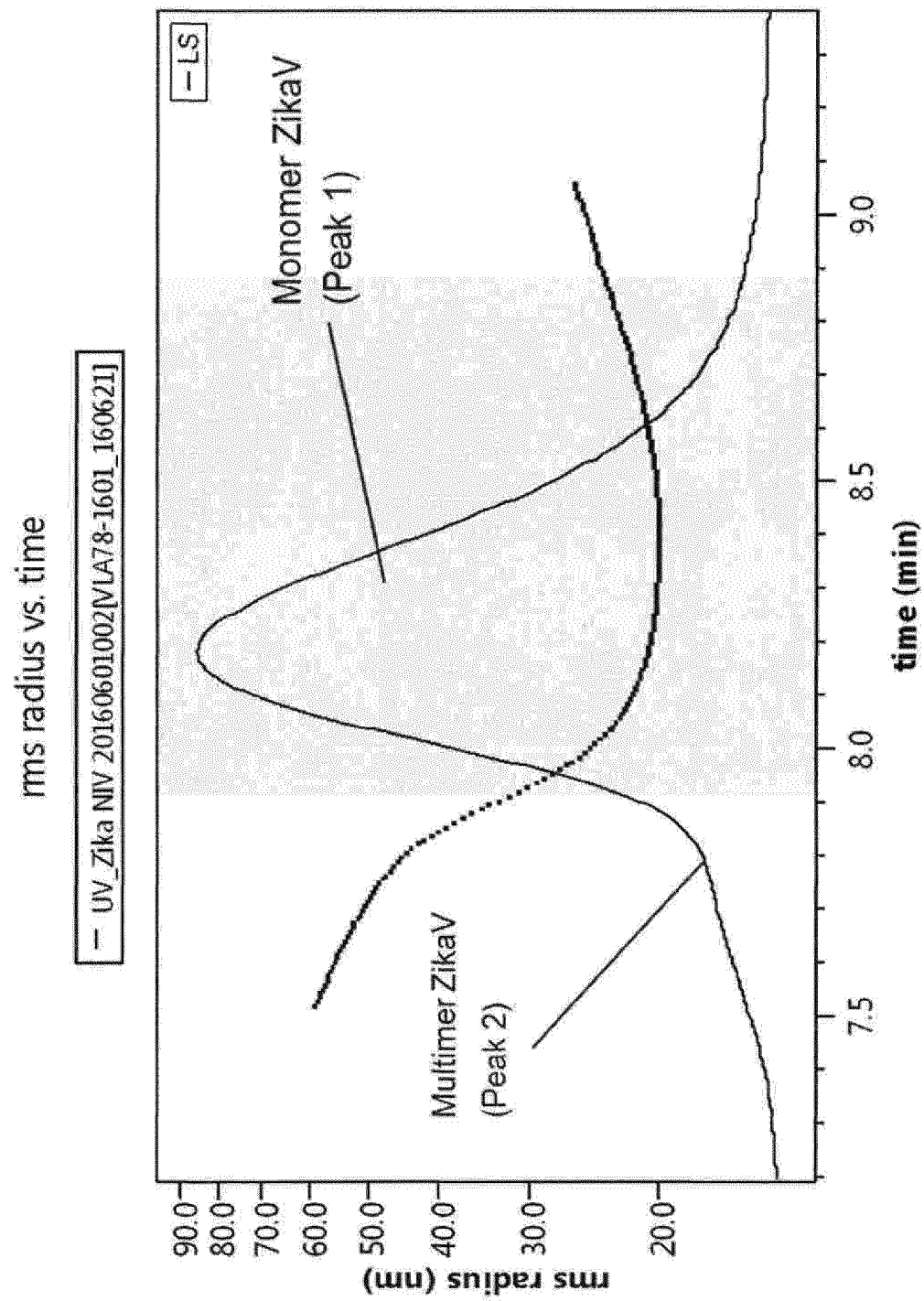
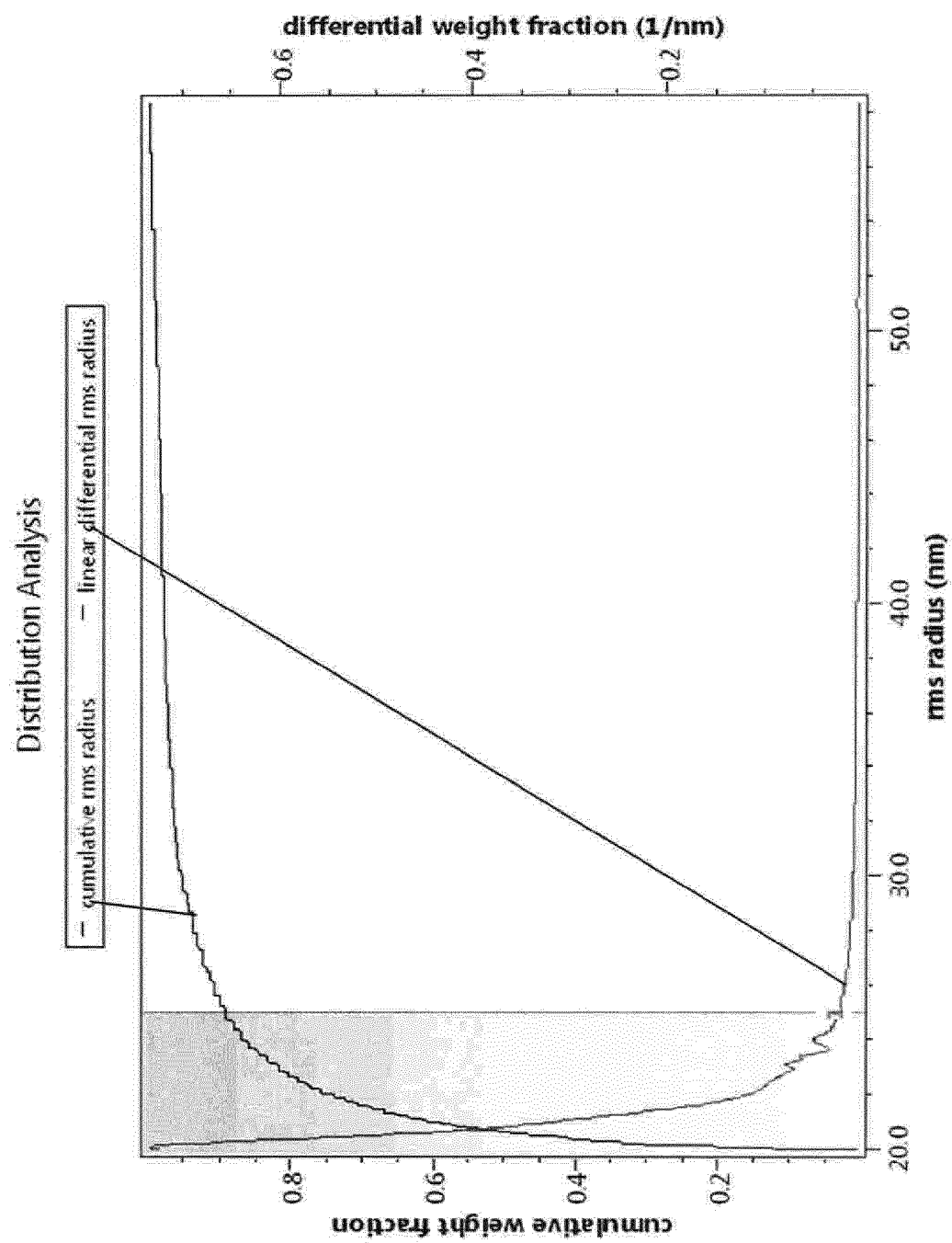


Figure 22



Bescheinigung

Die angehefteten
Unterlagen stimmen mit der
als ursprünglich eingereicht
geltenden Fassung der auf
dem nächsten Blatt
bezeichneten europäischen
Patentanmeldung überein.

Certificate

The attached documents are
exact copies of the text in
which the European patent
application described on the
following page is deemed to
have been filed.

Attestation

Les documents joints à la
présente attestation sont
conformes au texte,
considéré comme
initialement déposé, de la
demande de brevet
européen qui est spécifiée à
la page suivante.

Patentanmeldung Nr.

Patent application No.

Demande de brevet n°

16176049.1 / EP16176049

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP16176049.

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.



V. Joseph

Anmeldung Nr:
Application no.: 16176049.1
Demande no. :

Anmeldetag:
Date of filing: 23.06.16
Date de dépôt :

Anmelder / Applicant(s) / Demandeur(s):

Valneva SE
World Trade Center Lyon, Tour Oxygène
10-12 Boulevard Marius Vivier Merle
69003 Lyon/FR

Bezeichnung der Erfindung / Title of the invention / Titre de l'invention:

(Falls die Bezeichnung der Erfindung nicht angegeben ist, oder falls die Anmeldung in einer Nicht-Amtssprache des EPA eingereicht wurde, siehe Beschreibung bezüglich ursprünglicher Bezeichnung.

If no title is shown, or if the application has been filed in a non-EPO language, please refer to the description for the original title.

Si aucun titre n'est indiqué, ou si la demande a été déposée dans une langue autre qu'une langue officielle de l'OEB, se référer à la description pour le titre original.)

VIRUS PURIFICATION

In Anspruch genommene Priorität(en) / Priority(Priorities) claimed / Priorité(s) revendiquée(s)

Staat/Tag/Aktenzeichen / State/Date/File no. / Pays/Date/Numéro de dépôt:

Am Anmeldetag benannte Vertragsstaaten / Contracting States designated at date of filing / Etats contractants désignées lors du dépôt:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL
PT RO RS SE SI SK SM TR

VIRUS PURIFICATION

FIELD OF THE INVENTION

The disclosure relates to methods for the purification of viruses for use in vaccines.

BACKGROUND OF THE INVENTION

Regulatory agencies such as the World Health Organization establish standards and guidelines for the production of pharmaceutical compositions administered to humans, such as vaccines, that limit quantity and components of the compositions. Meeting these standards is particularly challenging with regard to production of vaccines containing biological agents, such as viruses, which must be propagated on cell substrates. Such vaccine preparations must be sterile (*i.e.*, free from independently replicating organisms) and may contain no more than 10 ng of host cell DNA per human dose, among other requirements. These standards are in place in order to ensure safety of the composition for human administration, but may introduce challenges in the development of processes used to produce such compositions.

Protamine was originally isolated from the sperm of salmon and other species of fish but is now produced primarily through recombinant biotechnology. It is a highly cationic peptide that binds to negatively charged molecules such as nucleic acids to form a stable ion pair. Its use in removing host cell nucleic acid is well document.

SUMMARY

During the course of routine virus purification, it was observed that addition of protamine sulfate to a virus harvest produced on a cell substrate removed not only contaminating DNA derived from host cells, as expected, but surprisingly also virtually eliminated immature and otherwise non-infectious virus particles from the preparation. This finding provides a streamlined, gentle, reproducible and broadly-applicable process for obtaining highly-purified infectious virus particles for applications such as vaccine preparation; furthermore, the process is not dependent on the charge of the virus particle.

Disclosed herein are downstream processes for purifying virus particles from a crude preparation. The downstream process can be applied to either a virus which has not adapted for propagation on a particular cell substrate or for a partial / fully cell substrate adapted virus particle.

Aspects of the invention provide processes for the purification of infectious virus particles comprising the steps of (a) providing a crude harvest (a) comprising virus particles and impurities, wherein the impurities are generated from growing said virus particles on a cell substrate; (b) reducing impurities from the crude harvest (a) by precipitation with an agent comprising a protamine salt, preferably a protamine sulphate, to obtain a virus preparation (b); and further purifying the virus preparation (b) by method or methods selecting for size of the virus particles, such as e.g. a sucrose density gradient centrifugation to obtain a virus preparation (c) comprising the infectious virus particles.

In some embodiments, the concentration of protamine sulphate in step (b) is about 1 to 10 mg/ml, more preferably about 1 to 5 mg/ml, more preferably about 1 to 2 mg/ml. In one embodiment, the concentration of protamine sulphate in step (b) is about 2 mg/mL. In one embodiment, the concentration of protamine sulphate is 1.2 to 1.8 mg/ml, more preferably 1.4 to 1.6 mg/ml. In a preferred embodiment, the concentration of protamine sulphate in step (b) is about 1.6 mg/ml or about 2 mg/ml.

In some embodiments, the residual host cell DNA of the virus preparation (e) is less than 1 µg/mL, especially less than 900, 800, 700, 600, 500, 400, 300 or 200 ng/mL, preferably less than 100 ng/mL. In a preferred embodiment, the residual host cell DNA of the virus preparation (c) is less than 10 ng/mL. In some embodiments, the residual host cell protein of the final virus preparation (c) is less than 10 µg/mL, especially less than 9, 8, 7, 6, 5, 4, 3 or 2 µg/mL, preferably less than 1 µg/mL. In a preferred embodiment, the residual host cell protein of the virus preparation (c) is less than 100 ng/mL. In some embodiments, the residual non-infectious virus particles of the final virus preparation (c) is less than 10 µg/mL, especially less than 9, 8, 7, 6, 5, 4, 3 or 2 µg/mL, preferably less than 1 µg/mL. In a preferred embodiment, the residual non-infectious virus particles of the virus preparation (c) is less than 100 ng/mL.

In some embodiments, the crude harvest (a) comprising the virus particles and impurities is subjected to one or more pre-purification step(s) prior to step (b). In some embodiments, the one or more pre-purification step(s) comprises digesting host cell genomic DNA in the crude harvest (a) comprising the virus particles and impurities by enzymatic treatment. In some embodiments, the one or more pre-purification step(s) comprises filtration, ultrafiltration, concentration, buffer exchange and/or diafiltration. In some embodiments, the one or more pre-purification steps is filtration using a filter having a pore size equal to or less than 1 μm . In some embodiments, the filter has a pore size equal to or less than 0.2 μm . In a preferred embodiment, the filter has a pore size of 0.2 μm . In some embodiments, the concentration and/or ultra/diafiltration and/or buffer exchange is performed by tangential flow filtration (TFF). In some embodiments, ultra/diafiltration of the crude harvest (a) comprising the virus particles and impurities is performed using a hollow fiber membrane having a cut-off of equal to or less than 300 kDa. In a preferred embodiment, the hollow fiber membrane has a cut-off of 100 kDa.

In some embodiments, the virus particle is a live virus, a chimeric virus, an attenuated live virus, a modified live virus, or a recombinant live virus. In a further step, the virus particles of the invention may be optionally inactivated. In some embodiments, the virus particle is an attenuated form of the virus particle. For example, the virus may have reduced infectivity, virulence, and/or replication in a host, as compared to a wild-type virus. In some embodiments, the virus is a mutated or modified virus, for example the nucleic acid of the virus may contain at least one mutation relative to the wild-type virus. In some embodiments, the virus is a recombinant live virus, meaning a virus that is generated recombinantly and may contain nucleic acid from different sources.

In some embodiments, the virus particle is a live virus, an attenuated live virus, a modified live virus, or a recombinant live virus. In some embodiments, the virus belongs to a virus family selected from the group consisting of Paramyxoviridae, Orthomyxoviridae, Flaviviridae, Filoviridae, Arenaviridae, Rhabdoviridae, and Coronaviridae. In some embodiments, the virus belongs to a virus family selected from the group consisting of Togaviridae (being live or inactivated), such as alphaviruses, or Flaviviridae (being live or

inactivated). In some embodiments, the virus is a virus of the family Flaviviridae, i.e. a flavivirus. In other embodiments, the virus is a Zika virus or Yellow Fever virus. In preferred embodiments, the virus is a Zika virus. In a most preferred embodiment, the Zika virus is a Zika virus from the Asian lineage.

In some embodiments, the relative reduction of impurity of the final virus preparation relative to the liquid medium (a) comprising the virus particles and impurities is in a range from 60 to 95%. In some embodiments, the residual impurity of the final virus preparation is less than 1%. We observed a decrease in the HCP peaks and the non-infectious aggregate peaks in the HPLC-SEC or SDS-PAGE. An exact quantification is difficult but one can measure the density of the SDS-PAGE bands and other methods.

In some embodiments, the filtration of step in (b)(ii) of claim 1 is performed using a filter having a pore size equal to or greater than 1 μm . In some embodiments, the filter has a pore size equal to or greater than 0.2 μm . In a preferred embodiment, the filter has a pore size of 0.2 μm .

In some embodiments, the virus is propagated in a cell line selected from the group consisting of an EB66 cell line, a Vero cell line, a Vero- α His cell line, a HeLa cell line, a HeLa-S3 cell line, a 293 cell line, a PC12 cell line, a CHO cell line, a 3T3 cell line, a PerC6 cell line, a MDSK cell line, a chicken embryonic fibroblast cell line, a duck cell line, and a diploid avian cell line. In some embodiments, said cell line is a duck cell line. In some embodiments, said cell line is a diploid avian cell line. In some embodiments, said cell line is EB66 cell line. In a preferred embodiment, said cell line is a Vero cell line.

Aspects of the invention provide a use of any of the processes described herein for manufacturing a composition for immunization against a viral infection. In a preferred embodiment, the composition is a vaccine. In one embodiment, the composition or vaccine is directed against Chikungunya virus. In one embodiment, the composition or vaccine is directed against a flavivirus. In one embodiment, the composition or vaccine is directed against Yellow Fever virus. In one embodiment, the composition or vaccine is directed against Zika virus such as e.g. a Zika virus of the Asian lineage.

Other aspects provide compositions comprising the virus particles obtainable by any of the processes described herein for treating and/or preventing a viral infection. In one embodiment, the viral infection is caused by Chikungunya virus. In one embodiment, the viral infection is caused by a flavivirus. In one embodiment, the viral infection is caused by Yellow Fever virus. In one embodiment, the viral infection is caused by Zika virus such as e.g. a Zika virus of the Asian lineage.

In some embodiments, the attenuated form of ChikV is derived from the LR2006-OPY1 ChikV infectious clone (La Reunion isolate). In some embodiments, the attenuated form of ChikV is the $\Delta 5nsP3$ mutant as described by Hallengård et al. (Novel Attenuated Chikungunya Vaccine Candidates Elicit Protective Immunity in C57BL/6 mice (2014) *Journal of Virology* 88(5):2858–2866) or an immunogenic variant thereof. The immunogenic variant of the $\Delta 5nsP3$ ChikV mutant is herein defined as having at least 80% sequence identity to the nucleotide sequence of the $\Delta 5nsP3$ mutant sequence, especially at least 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or at least 99% sequence identity.

In some embodiments, the Zika virus is derived from the Asian lineage. In some embodiments, the Zika virus is a Zika virus as described partially or fully in Sequence section of this application, i.e. any of sequences SEQ ID Nos 2 to 69, in particular all partly or fully described Zika viruses of the Asian lineages or an immunogenic variant thereof. The immunogenic variants of the Zika virus or Zika virus of the Asian lineages are herein defined as having at least 80% sequence identity to the nucleotide sequence of the sequences described in any of sequences SEQ ID Nos 2 to 69, especially at least 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or at least 99% sequence identity.

In some embodiments, the process of the invention results in an enrichment of infectious virus particles from the crude harvest comprising infectious virus particles and non-infectious virus particles and other virus products such that the enrichment of the infectious virus particles is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, preferably at least 80%, especially 85% relative to the total virus particle content of the crude harvest (a) comprising the virus particles and impurities.

In some embodiments, the residual impurity of the final virus preparation with respect to all impurities in the crude harvest is less than 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, preferably less than 5% as determined by SEC-HPLC (Size Exclusion Chromatography – HPLC).

In some embodiments, the filtration step of the virus preparation (b) after contact with the solid-phase matrix is performed using a filter having a pore size equal to or greater than 1 μm . In some embodiments, the filter has a pore size equal to or greater than 0.2 μm . In a preferred embodiment, the filter has a pore size of about 0.2 μm , such as 0.22 μm .

In some embodiments, the Zika virus, or Chikungunya virus is propagated in a cell line selected from the group consisting of an EB66 cell line, a Vero cell line, a Vero- α His cell line, a HeLa cell line, a HeLa-S3 cell line, a 293 cell line, a PC12 cell line, a CHO cell line, a 3T3 cell line, a PerC6 cell line, a MDSK cell line, a chicken embryonic fibroblast cell line, a duck cell line, and a diploid avian cell line. In some embodiments, said cell line is a duck cell line. In some embodiments, said cell line is a diploid avian cell line. In some embodiments, said cell line is EB66 cell line. In a preferred embodiment, said cell line is a Vero cell line.

Aspects of the invention provide a use of any of the processes described herein for manufacturing a composition for immunization against a Zika virus, Yellow Fever, or Chikungunya virus infection. In a preferred embodiment, the composition is a vaccine. In preferred embodiments, the vaccine is administered to the subject once, twice or three or more times. In a preferred embodiment, the vaccine is administered once or twice. In a preferred embodiment, the vaccine is administered only once.

Other aspects provide compositions comprising the virus particles obtainable by any of the processes described herein for treating and/or preventing a Chikungunya virus infection.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings are not intended to be drawn to scale. The Figures are illustrative only and are not required for enablement of the disclosure. For purposes of clarity, not every component may be labeled in every drawing. In the drawings:

Figure 1 shows the process of flavivirus maturation in the host cell. Full maturation of the particles requires proteolytic cleavage of the precursor membrane glycoprotein (prM) by the host protease furin. Not all prM molecules are cleaved, resulting in the release of mature, mosaic or immature-like conformations from the cells. Mosaic and immature forms are generally not infectious—only mature virions are infective and have hemagglutinin (HA) / TCID₅₀ activity. (Figure adapted from Plevka, et al., Maturation of flaviviruses starts from one or more icosahedrally independent nucleation centres, EMBO reports (2011) 12, 602–606).

Figure 2 shows schematically the genome of the ChikV, including non-structural and structural proteins (labeled “CHIKV”) as well as a schematic representation of the Δ5nsP3 attenuated Chikungunya virus used to exemplify the purification process of the current invention (labeled “Δ5nsP3”). The triangle indicates the approximate location of the deletion in the nsP3 coding region. (Figure adapted from Hallengård et al. 2014, *supra*.)

Figure 3 shows a flow-chart of an exemplary ChikV vaccine downstream purification process from the crude harvest to formulation of the drug substance, a preferred embodiment of the process of the invention.

Figure 4 shows the 214 nm, 260 nm and 280 nm absorbance of the individual SGC fractions of a representative purification run of the process of the invention (A); the SEC-HPLC analysis of the final pooled fractions containing purified infectious ChikV virus particles (B); and a silver-stained SDS-PAGE gel showing the protein content of the virus preparation following different steps of the process of the invention (defined in the table below the figure) (C). The SGC purified pool consisting of SGC fractions F7-F11 is shown in lane 12.

Figure 5 relates the SEC area (mAU*min; right axis) and TCID₅₀ results (log TCID₅₀/mL; left axis) of ChikV production harvests before and after PS treatment. The grey portions of the bars indicate large losses in SEC area following PS treatment, but no corresponding change in the total number of infectious particles (indicated by black portions of the bars) (A); SEC profile

of virus preparation before and after PS addition, showing a complete removal of large size virus aggregates by PS treatment as well as a reduction in host cell proteins (HCP) and LMW impurities (B).

Figure 6 shows electron micrographs of ChikV harvest before and after PS treatment.

Figure 7 shows relative amounts of ChikV particles and other components by SEC-HPLC analysis at the different steps of the process of the invention including, from top to bottom: crude harvest (a); 10X concentrated harvest; diafiltrated harvest; PS treated material; CC700-treated material and SGC purified pool.

Figure 8 shows a flow-chart of an exemplary Zika vaccine downstream purification process from the crude harvest to formulation of the drug substance, a preferred embodiment of the process of the invention.

Figure 9: Change in SEC profile of virus peak after PS addition showing a complete removal of large size aggregates and LMW impurities.

Figure 10: PS treatment results in selective removal of Zika virus aggregates and Vero HCP and LMW impurities (SEC-HPLC of 30x concentrated Zika Virus harvest day 5)

DETAILED DESCRIPTION OF THE INVENTION

Disclosed herein are processes for the purification of infectious virus particles, i.e., mature, functional virus particles, e.g. flavivirus particles (Yellow Fever, Zika Virus) and/or alphavirus particles (Chikungunya virus). The processes disclosed are characterized by the removal of undesired by-products of virus production on host cells, such as non-infectious virus particles and aggregated and immature virus by-products. The processes provided herein allow the production of highly-purified virus preparations comprising mostly infectious virus particles.

During the course of the invention, it was observed that protamine sulphate, added to remove contaminating DNA during virus purification, resulted not only in removal of contaminating DNA, but also in the loss of a high percentage of total virus particles present in the preparation. Surprisingly, however, quantification of total infectious virus particles by TCID50 before and after PS treatment revealed that the absolute number of infectious virus particles did not change following this loss of total virus particles. This observation clearly shows that treatment with PS can facilitate selective removal of non-infectious, aggregated and immature viral by-products, leaving behind the infectious Chikungunya virus particles. Because by-products produced during virus growth on host cells may have different (and undesirable) immunological properties or other unwanted side-effects or safety issues, a simple and robust way to remove these by-products is of high importance for the quality and safety of the final product.

Protamines are small arginine-rich nuclear proteins, present in high amounts in the sperm of fish, which have an important role in DNA packaging during spermatogenesis. Protamine sulfate (or "protamine" or "PS") can form a stable ion pair with heparin and is thus commonly used during certain surgeries when the anti-coagulation effect of heparin is no longer needed. In large doses, protamine sulfate administered alone can also have a weak anticoagulant effect ("Protamine sulfate". Wikipedia: The Free Encyclopedia. Wikimedia Foundation, Inc. 30 Sep 2015 Web. 26 Nov 2015 <https://en.wikipedia.org/wiki/Protamine_sulfate>). Protamine Sulphate is additionally routinely used in biotechnology applications such as DNA precipitation (e.g., removal of host cell DNA from cell culture processes), purification of DNA binding proteins and retroviral-mediated gene transfer.

Protamine is obtained from salmon sperm or produced recombinantly and is used as a sulphate salt. The four major peptides, which constitute almost the entire nitrogen-containing material in salmon protamine, have been fully characterized and found to be polypeptides of 30–32 amino acids in length, of which 21–22 residues are arginine. The average molecular mass is in the range of 4250 Da for the following sequence: PRRRRSSSRP VRRRRRPRVS RRRRRRGRRR RR (SEQ ID NO: 1). Herein, protamine is also referred to as protamine salt, or preferably protamine sulphate.

The present invention relates to the use of protamine sulphate (PS) in a process of purification of a live virus, wherein the protamine sulphate facilitates the removal of impurities from a crude virus harvest, including non-infectious virus particles and aggregates. As seen in Fig. 1, virus production in the host cell can result in the release of virus products which are not mature, infectious particles, which can also be considered impurities according to the present invention. As such, the present invention also relates to the enrichment of infectious virus particles from a crude harvest containing a mix of virus particles and other viral products in various stages of maturation.

The use of protamine sulphate can follow crude cell lysis or any further step after cell lysis wherein the virus particles are further enriched or concentrated and/or other impurities are removed and/or buffer components are exchanged. The further steps may comprise filtration or concentration of the crude cell lysate.

The protamine sulphate may comprise the sequence PRRRRSSSRP VRRRRRPRVS RRRRRRGGR RR (SEQ ID NO: 1) or a variant thereof wherein the amino acid sequence comprises from 28-35 amino acids, preferably 29-34, more preferably 30-33 amino acids, most preferably 31 or 32 amino acids. The protamine sulphate preferably comprises at least 19 arginine residues, more preferably at least 20 arginine residues, more preferably at least 21 arginine residues, even more preferably at least 22 residues, most preferably 20 or 21 arginine residues. Further, other protamine sulphate-like compounds or variants thereof may be used. Therefore, the use of the term "protamine salt" herein shall serve to encompass natural variations on SEQ ID NO: 1, preferably, but not limited to, the protamine sulphate forms.

The process comprising the use of protamine sulphate of the invention can be applied to purification of any virus for use in pharmaceutical compositions, for example, for a pharmaceutical composition such as a vaccine where it is important that the virus is in its infectious form. The virus to be purified may be any live virus, any live attenuated virus or any live chimeric virus, preferably a live wild type virus such as a Zika virus of the Asian lineage. In one embodiment, the virus particle is also be later inactivated. In a preferred embodiment, the virus is inactivated with formaldehyde.

In a preferred embodiment, the produced Zika virus is derived from the Asian lineage (which includes the strains found in South America and all strains derived from any Asian lineage). In some other embodiments, the produced Zika virus is a Zika virus as described in the Sequence section of this application (SEQ ID NO: 2 to 69).

In another preferred embodiment, the live attenuated Chikungunya virus is the protective ChikV-ICRES1-Δ5nsP3 described by Hallengård *et al.* (Novel Attenuated Chikungunya Vaccine Candidates Elicit Protective Immunity in C57BL/6 mice (2014) *J. Virology*, 88(5):2858–2866). Briefly, the ChikV genome carries a positive-sense single-stranded RNA genome of 11 Kb containing two open reading frames encoding nonstructural proteins (nsP1 to nsP4) and structural proteins (C, E3, E2, 6K, and E1), respectively (see Fig. 2, top construct). The attenuated virus Δ5nsP3, based on the La Reunion ChikV strain LR2006-OPY1, was obtained by the substitution of amino acid residues 1656 to 1717 of the P1234 polyprotein with a small linker (aa sequence AYRAAAG) in the hypervariable region of the nsP3 protein (see Fig. 2, bottom construct). The Δ5nsP3 ChikV mutant was shown to be infectious, highly immunogenic and protective against challenge with wild type ChikV (Hallengård, *et al.*, *supra* and Hallengård, *et al.*, Prime-Boost Immunization Strategies against Chikungunya Virus (2014) *J. Virology*, 88(22):13333-13343). In one embodiment, the live attenuated Chikungunya virus may be a variant of the ChikV-ICRES1-Δ5nsP3 attenuated mutant virus.

A preferred embodiment of the process of the current invention is shown in Figure 3 (Chikungunya virus) and Figure 10 (Zika virus).

Table 1. Overview of process buffers and stock solutions

Buffer	Composition	Final pH	Final conductivity [mS/cm]
A	0.5 M NaOH		n.a.
B	0.1 M NaOH		n.a.
C	25 mM Tris, 150 mM NaCl	7.4±0.2	16.5
D	1 M Tris	7.4±0.2	n.a.
E	4.5 M NaCl	n.a.	n.a.
F	1 M NaCl	n.a.	n.a.
G	1 % SDS	n.a.	n.a.
H	50 % (w/w) Sucrose in 25 mM Tris, 150 mM NaCl	7.4±0.2	n.a.
I	35 % (w/w) Sucrose in 25 mM Tris, 150 mM NaCl	7.4±0.2	n.a.
J	15 % (w/w) Sucrose in 25 mM Tris, 150 mM NaCl	7.4±0.2	n.a.

K	10 x PBS	7.4±0.2	n.a.
L	50 mg/mL Protamine sulphate	7.4±0.2	n.a.
M	Drug substance formulation buffer (10mM Tris(hydroxymethyl)-aminomethan, 5 % Sucrose, 1% (10 mg/mL) rHSA)	7.4±0.2	1.3

Table 2. Abbreviations

CC700	Capto™ Core 700
ChikV	Chikungunya virus
EtOH	Ethanol
EU	Endotoxin units
DS	Drug Substance
DP	Drug Product
DSP	Downstream Process
HCP	Host cell protein
hcDNA	Host cell DNA
hpi	Hours post infection
HPLC	High Pressure Liquid Chromatography
ID	Inner diameter
LDS buffer	Lithium dodecyl sulfate sample loading buffer
MALLS	Multangle light scattering
mAU	Milli absorbance units
PD	Process development
PFU	Plaque forming units
SEC	Size exclusion chromatography
SGC	Sucrose gradient centrifugation
SDS	Sodium dodecyl sulphate
TBS	Tris buffered saline
TFF	Tangential flow filtration
TCID50	Tissue culture infectious dose 50%
UF/DF	Ultrafiltration/diafiltration
rcf	Relative centrifugal force
rHSA	Recombinant human serum albumin

SEQUENCES

The amino acid sequence of a typical form of protamine is provided by SEQ ID NO: 1:

PRRRSSSRP VRRRRRPRVS RRRRRRGRR RR.

Provided below are examples of nucleic acid sequences of the genomes of Zika viruses that may be used in the methods, compositions, and/or vaccines described herein.

KU321639.1 Zika virus strain ZikaSPH2015, Brazil, complete genome (SEQ ID NO: 2)

GTTGTTACTGTTGCTGACTCAGACTGCGACAGTTCGAGTTTGAAGCGAAAGCTAGCAACAGTATCAACAGGTTTTATTTGGATT
 TGGAAACGAGAGTTTCTGGTCATGAAAAACCCAAAAAGAAATCCGGAGGATTCCGGATTGTCAATATGCTAAAACGCGGAG
 TAGCCCGTGTGAGCCCTTTGGGGGCTTGAAGAGGCTGCCAGCCGGACTTCTGCTGGGTCTATGGGCCCATCAGGATGGTCTTG
 GCAATTCTAGCCTTTTTGAGATTCACGGCAATCAAGCCATCACTGGGTCTCATCAATAGATGGGGTTCACTGGGGAAAAAGA
 GGCTATGGAAATAATAAGAAGTTCAAGAAAGATCTGGCTGCCATGCTGAGAATAATCAATGCTAGGAAGGAGAAGAAGAG
 ACGGGGCGCAGATACTAGTGTGGAATTGTTGGCCTCTGCTGACCACAGCTATGGCAGCGGAGGTCACTAGACGTGGGAGT
 GCATACTATATGTACTTGGACAGAAACGATGCTGGGGAGGCCATATCTTTCCAACCACATTGGGGATGAATAAGTGTATAT
 ACAGATCATGGATCTTGGACACATGTGTGATGCCACCATGAGCTATGAATGCCCTATGCTGGATGAGGGGGTGAACCAGAT
 GACGTGATTGTTGGTGCAACACGACGTCAACTTGGGTTGTGTACGGAACCTGCCATCAGAAAAAGGTGAAGCACGGAGAT
 CTAGAAGAGCTGTGACGCTCCCTCCCTCCCTCACTAGGAAGCTGCAACGCGGTGCAAACTGTTGGAATCAAGAGAATAC
 ACAAAGCACTTGATTAGAGTCGAAAATTGGATATTAGGAACCTGGCTTCGCGTTAGCAGCAGCTGCCATCGCTTGGCTTTG
 GGAAGCTCAACGAGCCAAAAAGTCATATACTTGGTCATGATACTGCTGATTGCCCGGCATACAGCATCAGGTGCATAGGAGT
 CAGCAATAGGGACTTTGTGGAAGGTATGTGAGGTGGGACTTGGGTTGATATTGTCTTGAACATGGAGGTTGTGTACCGTA
 ATGGCACAGGACAAACCGACTGTGACATAGAGCTGTTACAACAACAGTCAGCAACATGGCGGAGGTAAGATCCTACTGCT
 ATGAGGCATCAATATCAGACATGGCTTCGACAGCCGCTGCCAACACAAGGTGAAGCCTACCTTGACAAGCAATCAGACACT
 CAATATGTCTGCAAAAGAACGTTAGTGACAGAGGCTGGGGAAATGGATGTGGACTTTTTGGCAAAGGGAGTCTGGTGACAT
 GCGCTAAGTTTGCATGCTCCAAGAAAATGACCGGAAGAGCATCCAGCCAGAGAATCTGGAGTACCGGATAATGCTGTCAGT
 TCATGGCTCCCGACAGTGGGATGATCGTTAATGACACAGGACATGAACTGATGAGAATAGAGCGAAGGTTGAGATAACG
 CCCAATTCACCAAGAGCCGAAGCCACCTGGGGGGTTTGGAAAGCCTAGGACTTGATTGTGAACCGAGGACAGGCCTTGACTT
 TTCAGATTGTATTACTTGACTATGAATAACAAGCACTGGTTGGTTACAAGGAGTGGTTCCACGACATTCCATTACCTTGGCAC
 GCTGGGGCAGACACCGGAATCCCACTGGAACAACAAGAAAGCACTGGTAGAGTTCAAGGACGCACATGCCAAAAGGCAA
 ACTGTGCTGGTTCTAGGGAGTCAAGAAGGAGCAGTTACACGGCCCTTGTGGAGCTCTGGAGGCTGAGATGGATGGTGCAA
 AGGGAAGGCTGTCTCTGGCCACTTGAAATGTGCGCTGAAATGGATAAACTTAGATTGAAGGGCGGTGCATACTCCTTGTGT
 ACCGCAGCGTTCACATTACCAAGATCCCGGCTGAAACACTGCACGGGACAGTCACAGTGGAGGTACAGTACGCAGGGACAG
 ATGGACCTTGCAAGGTTCCAGCTCAGATGGCGGTGGACATGCAAACTCTGACCCAGTTGGGAGGTTGATAACCGCTAACCCC
 GTAATCACTGAAAGCACTGAGAACTCTAAGATGATGCTGGAACCTTGATCCACCATTTGGGGACTCTTACATTGTATAGGAGTC
 GGGGAGAAGAAGATCACCCACCACTGGCAGAGGAGTGGCAGCACCATTGGAAGGCAATTTGAAGCCACTGTGAGAGGTGCC
 AAGAGAAATGGCAGTCTTGGGAGACACAGCCTGGGACTTTGGATCAGTTGGAGGCGCTCTCAACTATTGGGCAAGGGCATCC
 ATCAAATTTTGGAGCAGCTTCAAATCATTGTTTGGAGGAATGTCTGTTCTCACAAATCTCATTGGAACGTTGCTGATGTG
 GTTGGGTCTGAACACAAAGAATGGATCTATTTCCCTTATGTGCTTGGCCTTAGGGGGAGTGTGATCTTCTATCCACAGCCGT
 CTCTGCTGATGTGGGGTGCTCGGTGGACTTCTCAAAGAAGGAGACGAGATGCGGTACAGGGGTGTTCTGCTATAACGACGTT
 GAAGCCTGGAGGGACAGGTACAAGTACCCTCTGACTCCCCCGTAGATTGGCAGCAGCAGTCAAGCAAGCCTGGGAAGATG
 GTATCTGCGGGATCTCTCTGTTTCAAGAATGGAAAACATCATGTGGAGATCAGTAGAAGGGGAGCTCAACGCAATCCTGGAA
 GAGAATGGAGTTCAACTGACGGTCTTGTGGGATCTGTAAAAACCCCATGTGGAGAGGTCCACAGAGATTGCCGTGCTG
 TGAACGAGCTGCCCCACGGCTGGAAGGCTTGGGGGAAATCGCACTTCGTCAGAGCAGCAAAGACAAATAACAGCTTTGTCGT
 GGATGGTGACACACTGAAGGAATGCCCACTCAAACATAGAGCATGGAACAGCTTCTTGTGGAGGATCATGGGTTGGGGTA
 TTTCACTAGTGTCTGGCTCAAGGTTAGAGAAGATTATTATTAGAGTGTGATCCAGCCGTTATTGGAACAGCTGTTAAGGGA
 AAGGAGGCTGTACACAGTGATCTAGGCTACTGGATTGAGAGTGAGAAGAATGACACATGGAGGCTGAAGAGGGCCCATCTG
 ATCGAGATGAAACATGTGAATGGCCAAAGTCCACACATTGTGGACAGATGGAATAGAAGAGAGTGATCTGATCATACCCA
 AGTCTTTAGCTGGGCCACTCAGCCATCACAATACCAGAGAGGGCTACAGGACCCAAATGAAAGGGCCATGGCACAGTGAAGA
 GCTTGAAATTCGGTTGAGGAATGCCAGGCACTAAGGTCCACGTGGAGGAAACATGTGGAACAAGAGGACCATCTCTGAGA

TCAACCACTGCAAGCGGAAGGGTGATCGAGGAATGGTGCTGCAGGGAGTGACAATGCCCCACTGTCGTTCCGGGCTAAAG
 ATGGCTGTTGGTATGGAATGGAGATAAGGCCAGGAAAGAACAGAAAGCAACTTAGTAAGGTCAATGGTGACTGCAGGATC
 AACTGATCACATGGATCACTTCTCCCTTGGAGTGCTTGATTCTGCTCATGGTGCAGGAAGGGCTGAAGAAGAGAATGACCA
 CAAAGATCATCATAAGCACATCAATGGCAGTGCTGGTAGCTATGATCCTGGGAGGATTTTCAATGAGTGACCTGGCTAAGCTT
 GCAATTTTGATGGGTGCCACCTTCGCGGAAATGAACACTGGAGGAGATGTAGCTCATCTGGCGCTGATAGCGGCATTCAAAGT
 CAGACCAGCGTTGCTGGTATCTTTCATCTTCAGAGCTAATTGGACACCCCGTGAAAGCATGCTGCTGGCCTTGGCCTCGTGCT
 TTTGCAAACCTGCGATCTCCGCTTGGAAGGCGACCTGATGGTTCTCATCAATGGTTTTGCTTTGGCCTGGTTGGCAATACGAGC
 GATGGTTGTTCCACGCACTGATAACATCACCTTGGCAATCCTGGCTGCTCTGACACCACTGGCCCGGGGCACACTGCTTGTGGC
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KU509998.1 Zika virus strain Haiti/1225/2014, Haiti, complete genome (SEQ ID NO: 5)

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