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(54) **ZIKA VIRUS VACCINES USING VIRUS-LIKE PARTICLES**

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C12N 7/00 (2006.01)

(52) **U.S. Cl.**

CPC ***A61K 39/12*** (2013.01); ***C12N 7/00*** (2013.01); *A61K 2039/55* (2013.01)

(57) **ABSTRACT**

A flavivirus virus-like particle and methods of making and using that particle, and antibodies raised to a plurality of those particles, are provided.

FIG. 1A.

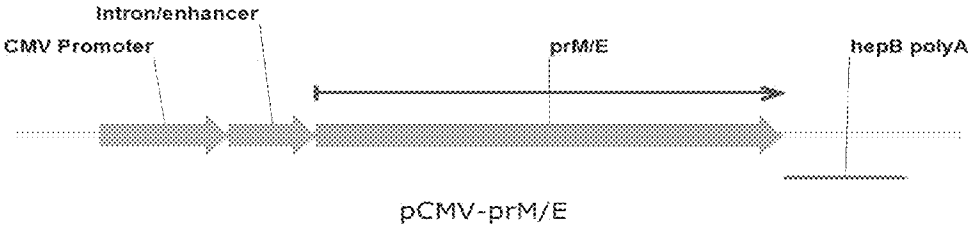

Intron/enhancer
CMV Promoter
prM/E
hepB polyA
pCMV-prM/E

FIG. 1B.

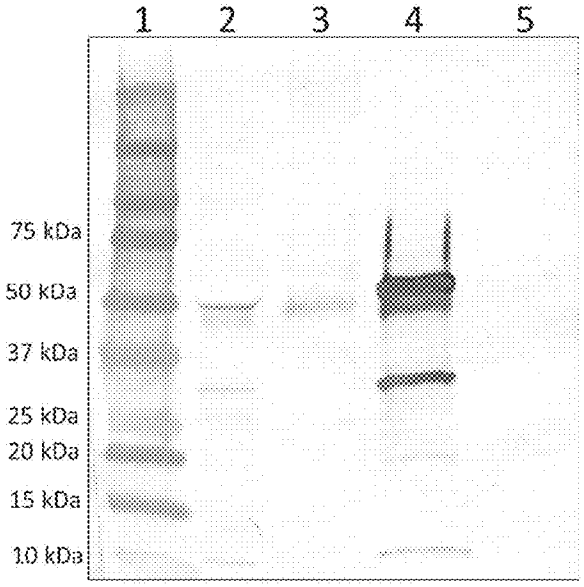

1
2
3
4
5
75 kDa
50 kDa
37 kDa
25 kDa
20 kDa
15 kDa
10 kDa

FIG. 1C.

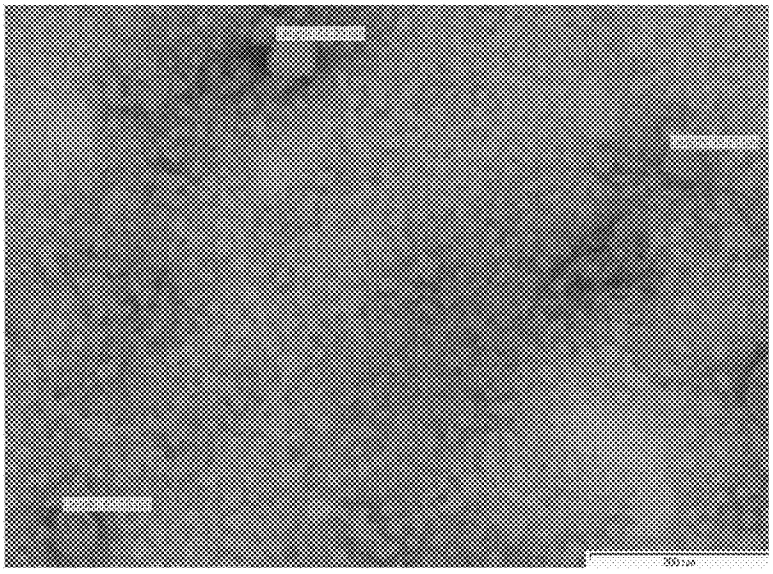


FIG. 1D.

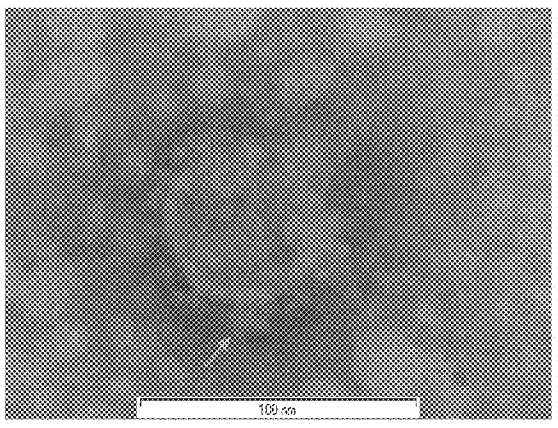


FIG. 1E.

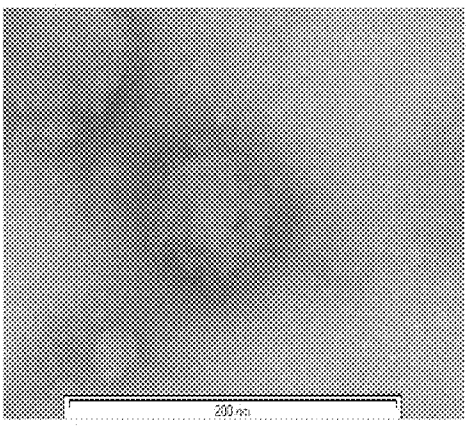


FIG. 2A.

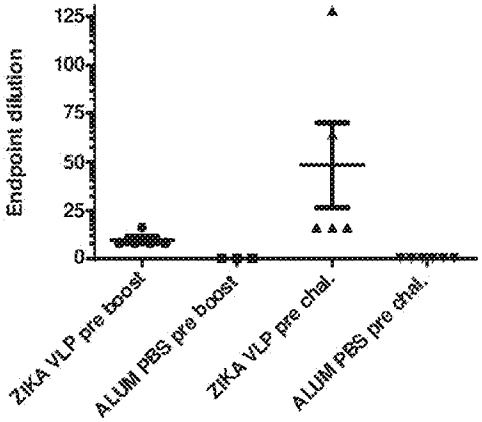


FIG. 2B.

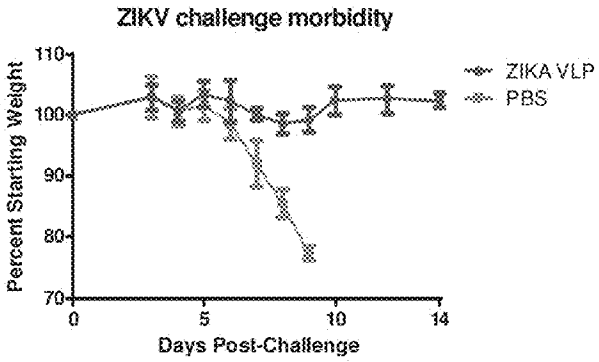


FIG. 2C.

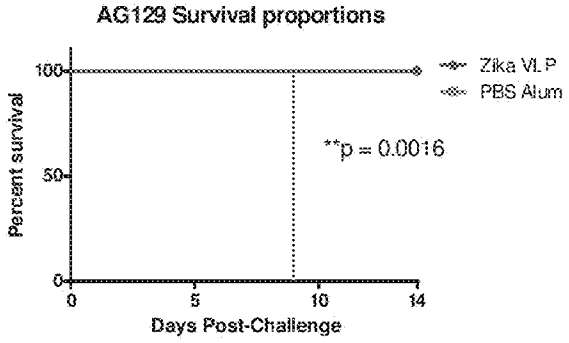


FIG. 2D.

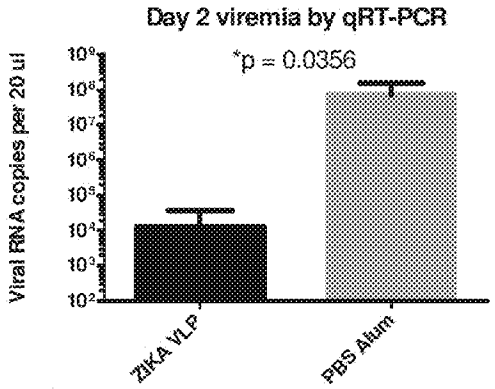


FIG. 2E.

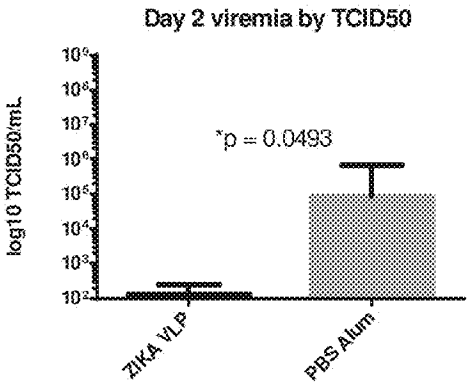


FIG 2F.

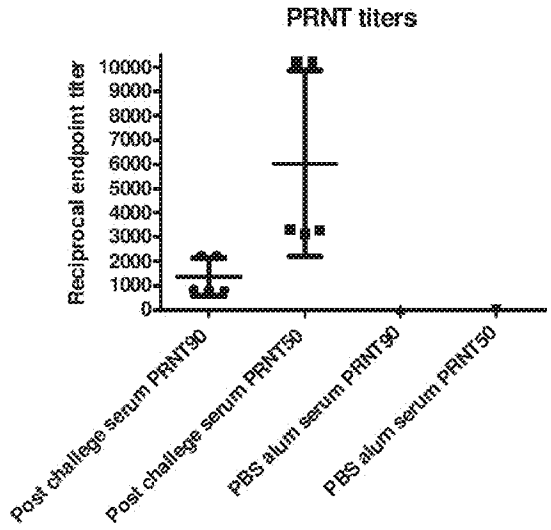


FIG. 3A.

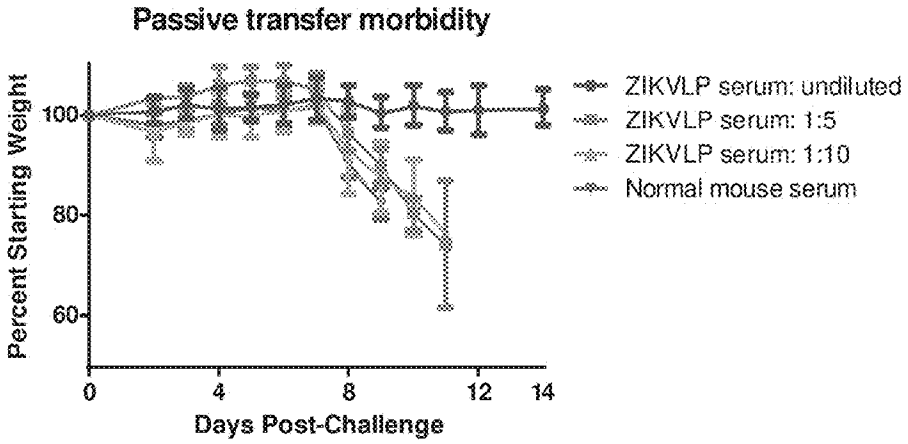

Passive transfer morbidity
Percent Starting Weight
100
80
60
0
4
8
12
14
Days Post-Challenge
ZIKVLP serum: undiluted
ZIKVLP serum: 1:5
ZIKVLP serum: 1:10
Normal mouse serum

FIG. 3B.

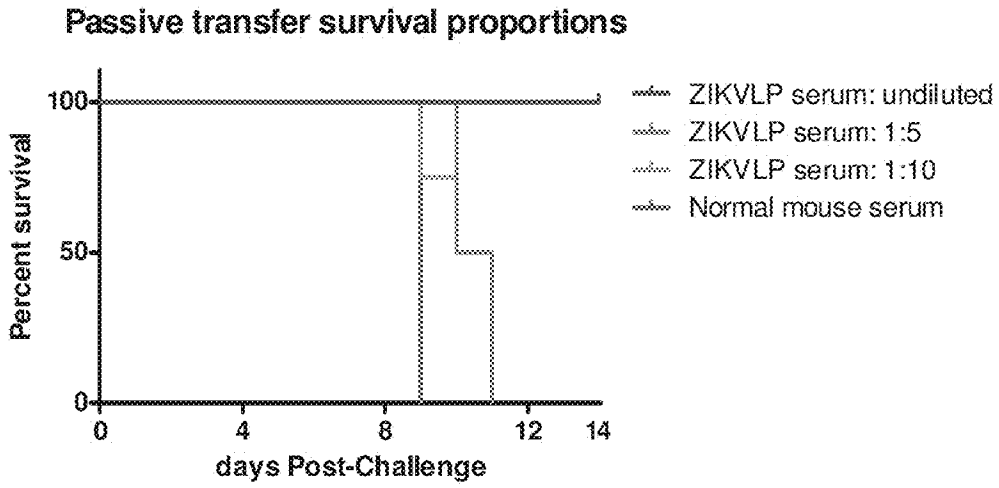

Passive transfer survival proportions
Percent survival
100
50
0
0
4
8
12
14
days Post-Challenge
ZIKVLP serum: undiluted
ZIKVLP serum: 1:5
ZIKVLP serum: 1:10
Normal mouse serum

FIG. 4

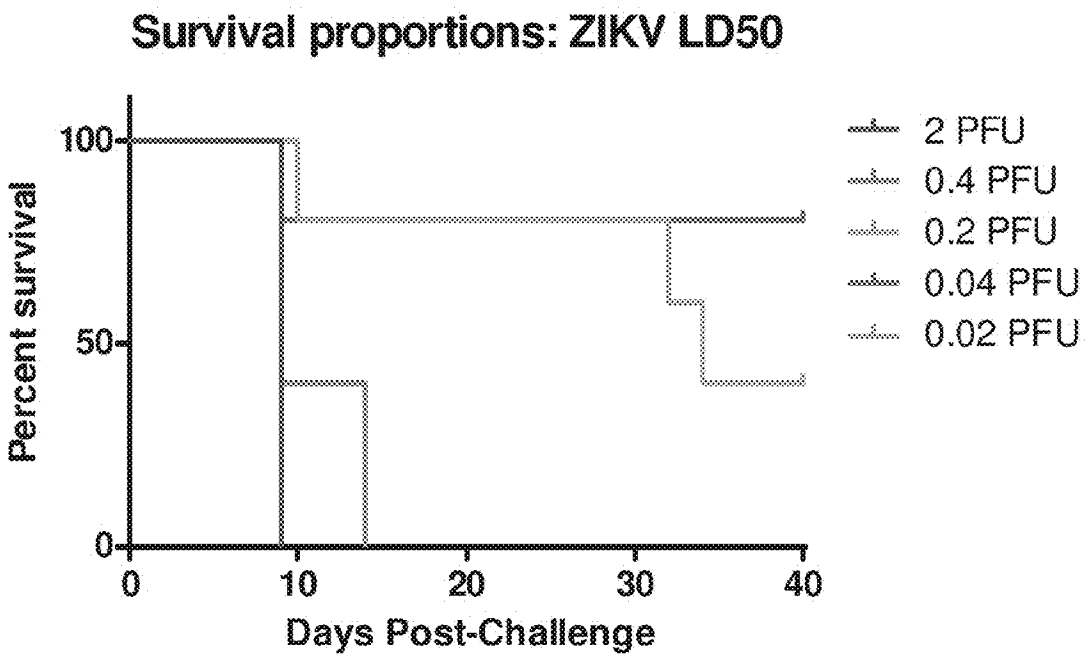

Survival proportions: ZIKV LD50
Percent survival
100
50
0
0
10
20
30
40
Days Post-Challenge
2 PFU
0.4 PFU
0.2 PFU
0.04 PFU
0.02 PFU

FIG. 5A

WEIGHT LOSS OF AG129 AFTER ID CHALLENGE WITH 20 PFU ZIKV OVER A 12 DAY PERIOD.

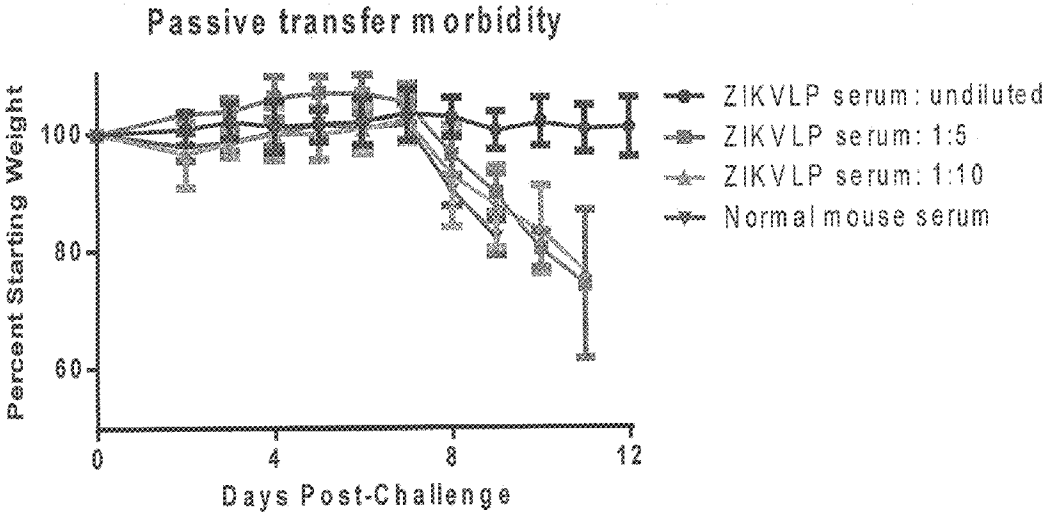
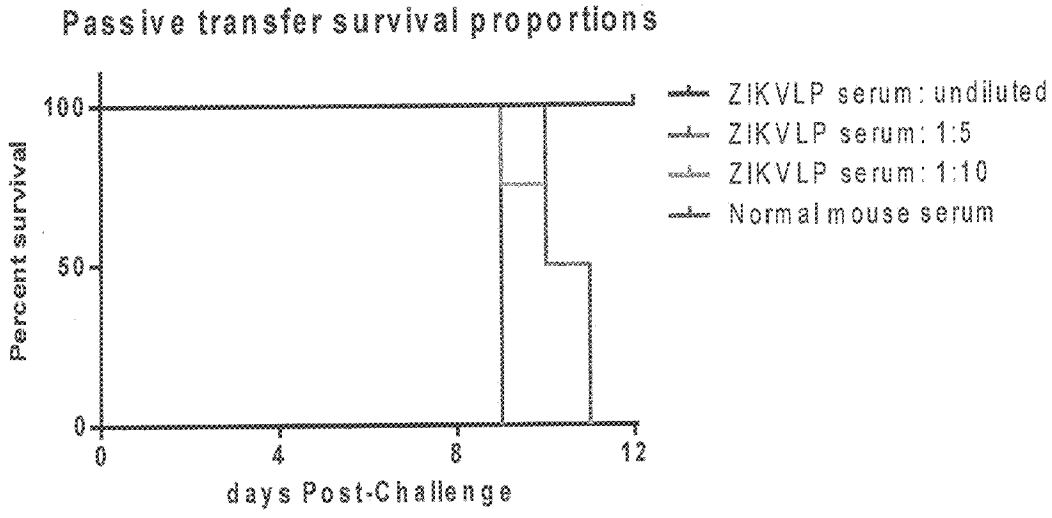


FIG. 5B

SURVIVAL OF AG129 AFTER ID CHALLENGE WITH 200 PFU ZIKV OVER A 12 DAY PERIOD.



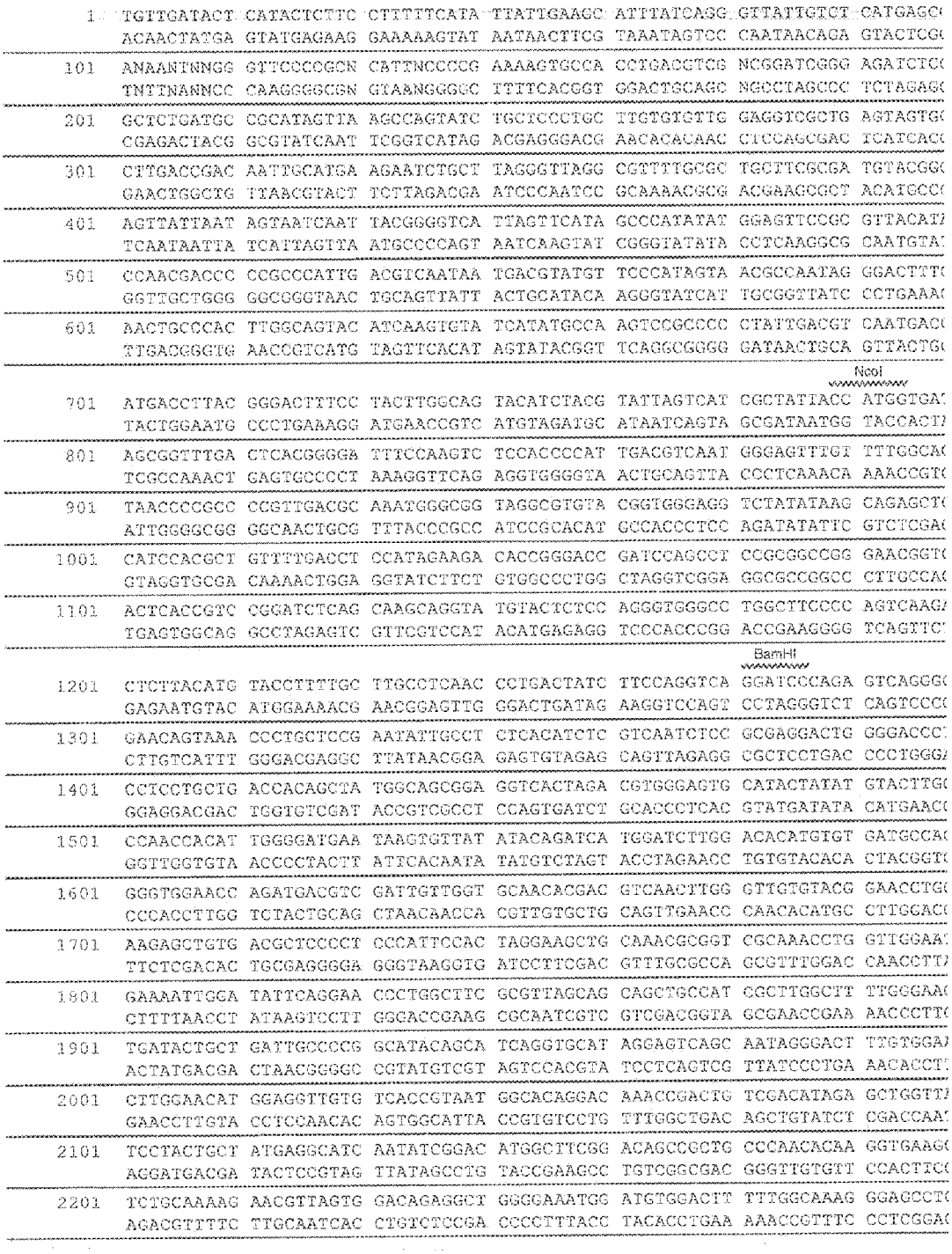


FIG. 6A

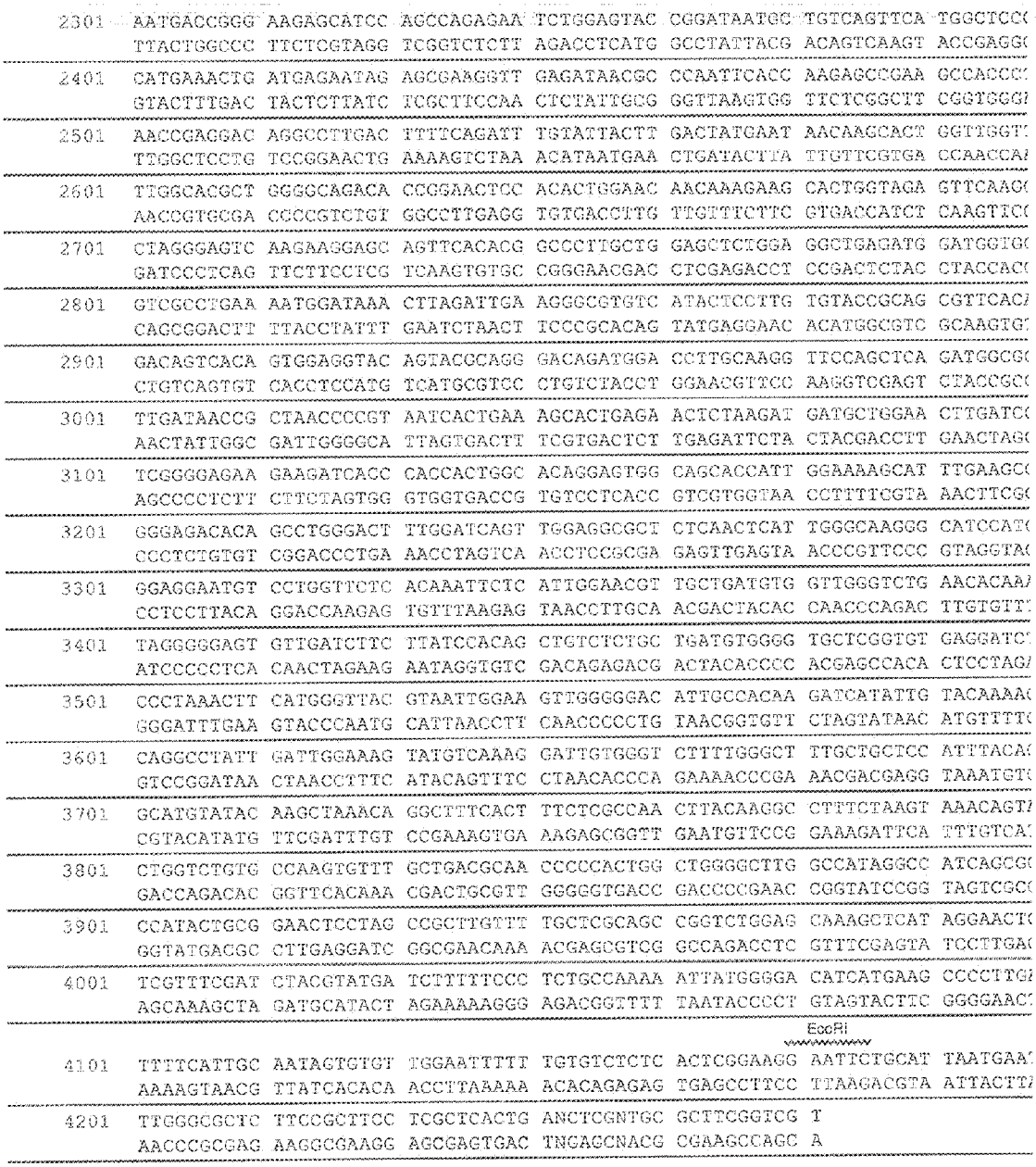


FIG. 6B

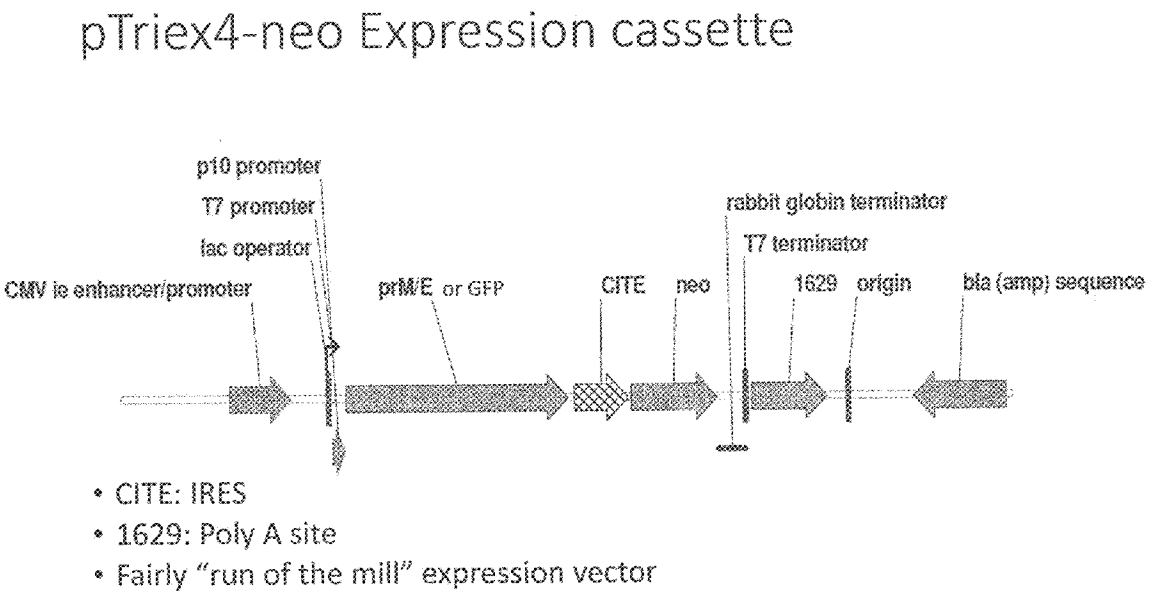

pTriex4-neo Expression cassette
p10 promoter
T7 promoter
lac operator
CMV ie enhancer/promoter
prM/E or GFP
CITE
neo
rabbit globin terminator
T7 terminator
1629
origin
bla (amp) sequence
• CITE: IRES
• 1629: Poly A site
• Fairly "run of the mill" expression vector

FIG. 7

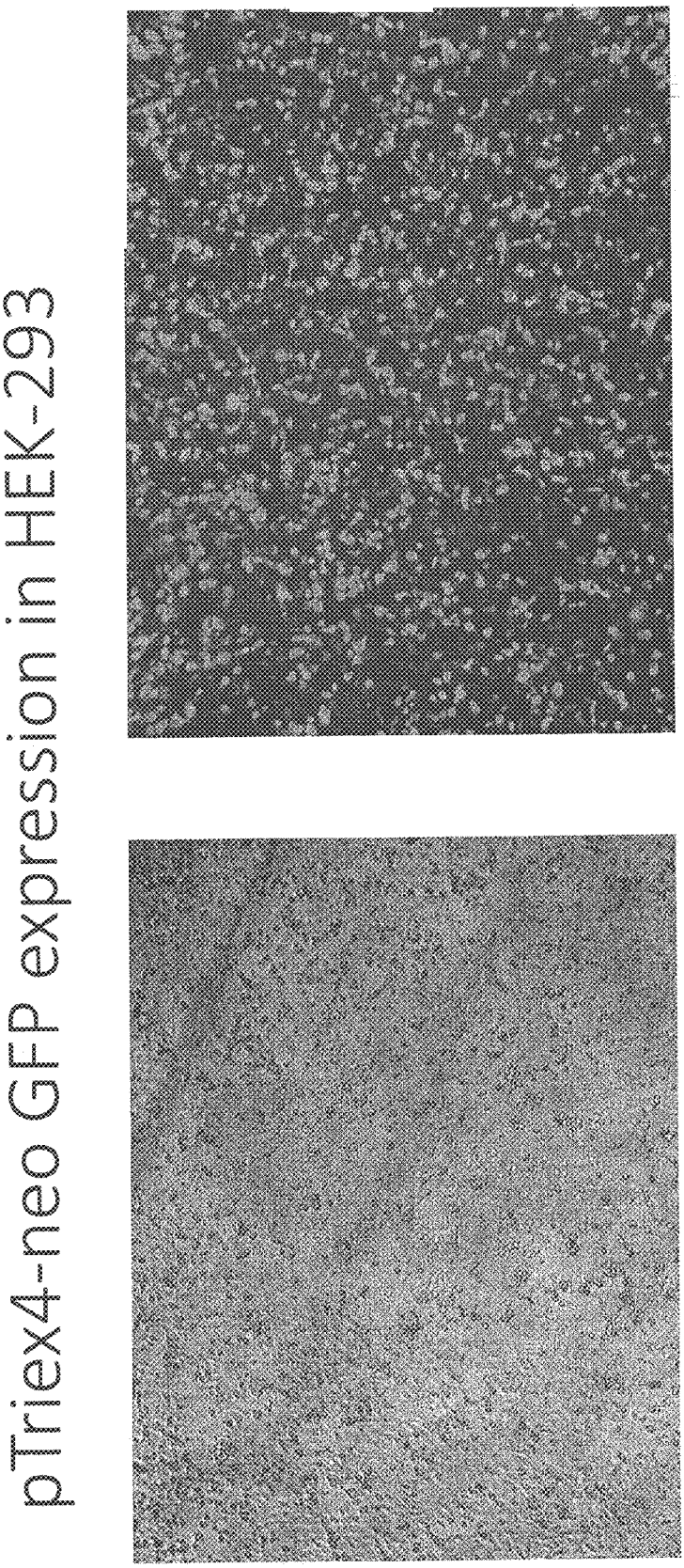


FIG. 8A

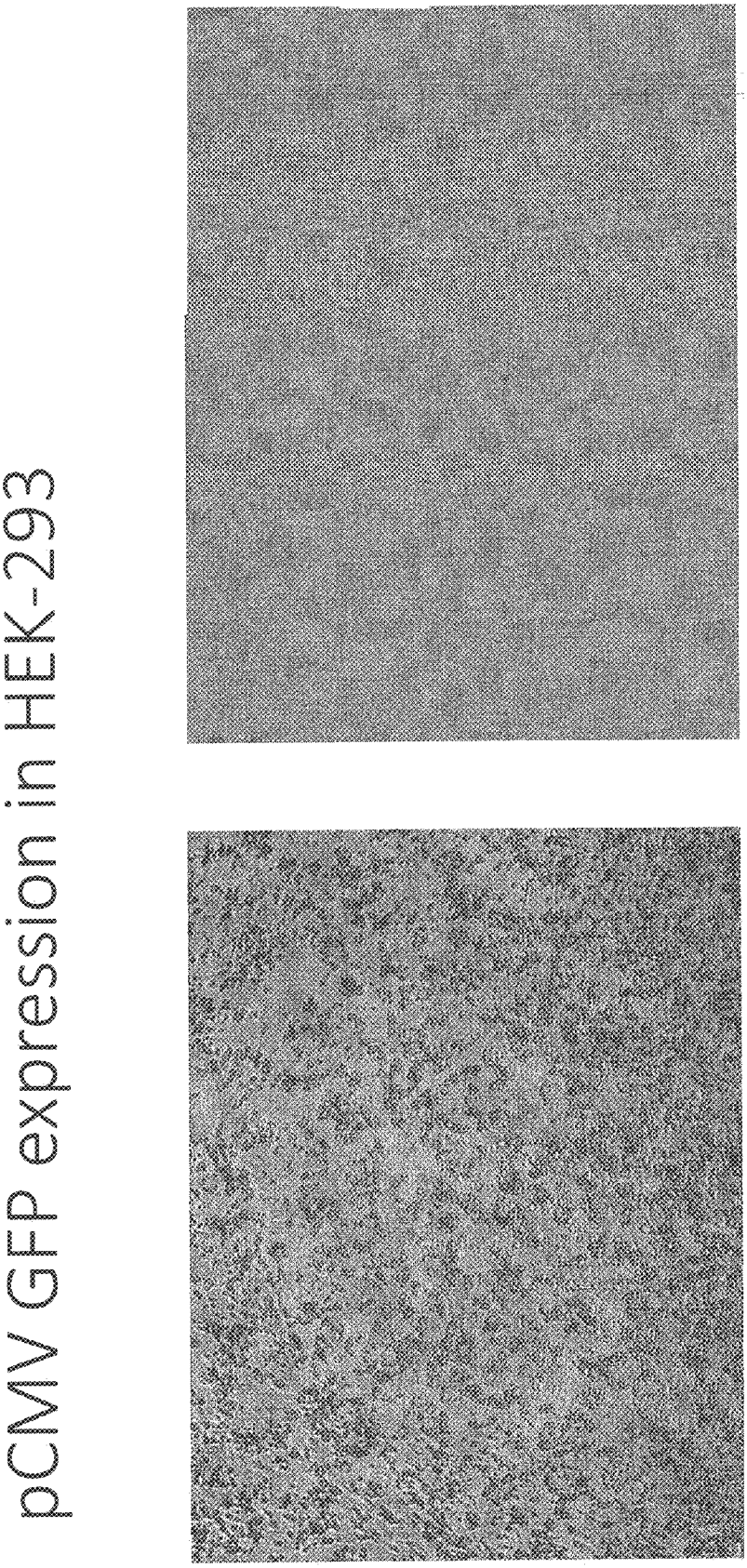
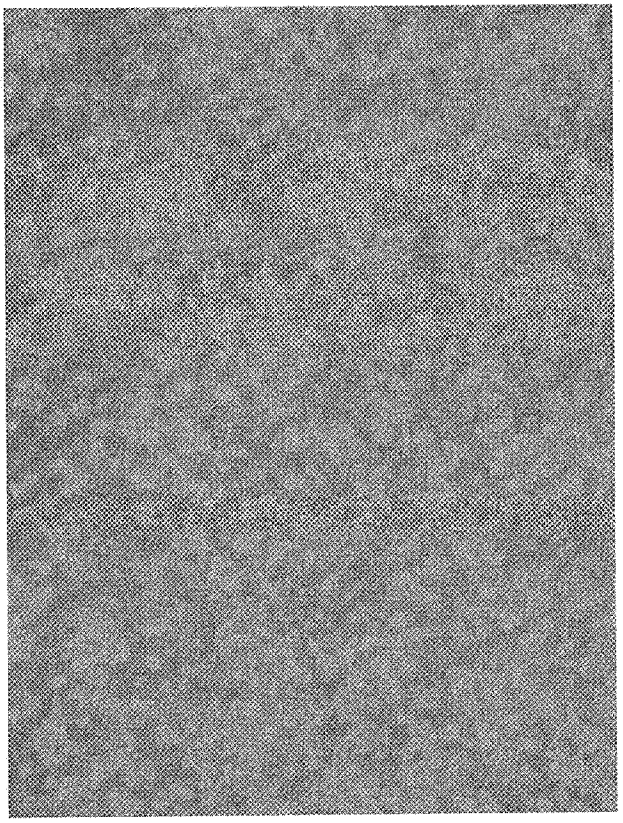
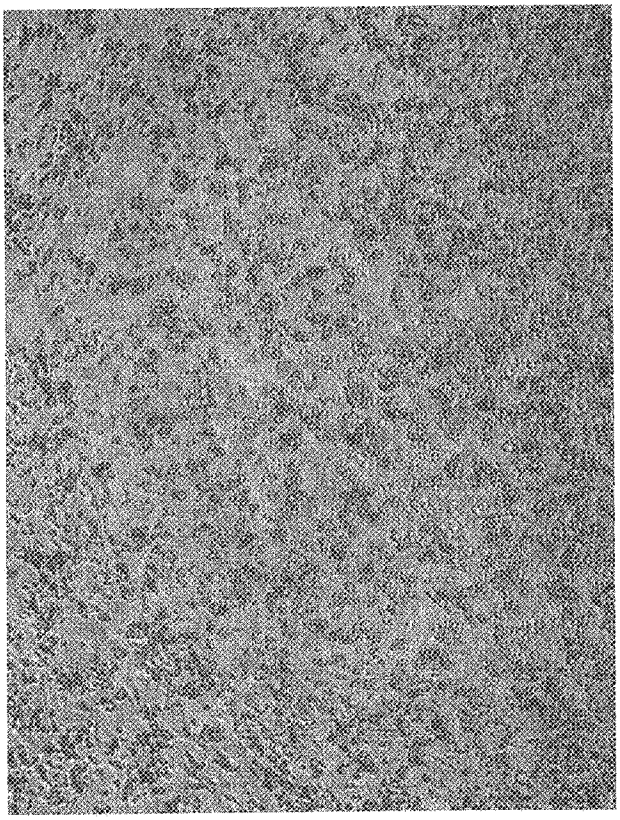


FIG. 8B

pCMV GFP expression in HEK-293





• Lamp turned down about 70%

FIG. 8C

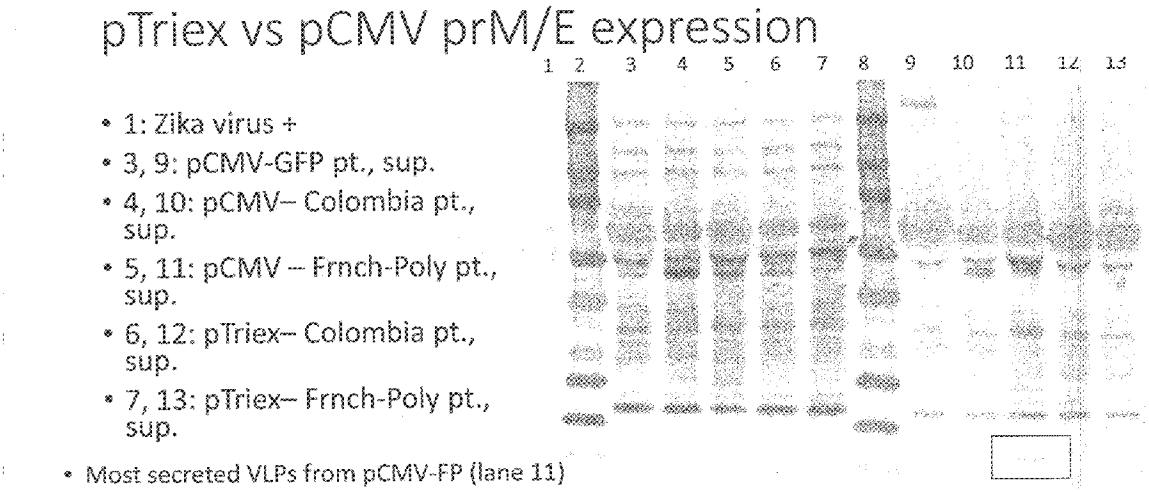

pTriex vs pCMV prM/E expression
1 2 3 4 5 6 7 8 9 10 11 12 13
• 1: Zika virus +
• 3, 9: pCMV-GFP pt., sup.
• 4, 10: pCMV– Colombia pt., sup.
• 5, 11: pCMV – Frnch-Poly pt., sup.
• 6, 12: pTriex– Colombia pt., sup.
• 7, 13: pTriex– Frnch-Poly pt., sup.
• Most secreted VLPs from pCMV-FP (lane 11)
• HEK cells transfected with plasmids, supernatant (sup.) and cells (pt.) harvested after 48 hours
• Sup. fraction was concentrated by centrifugation at 100,000g for 60'
• Western using UTMB mouse ascites

FIG. 9

Preliminary studies in mice

- Mice were injected IP with ~10^6 TCID50 of ZIKV
- 5 weeks later bleed, then injected with crude VLP supernatant
- Mice were bled 7 days after injection and antibodies analyzed by ZIKV ELISA

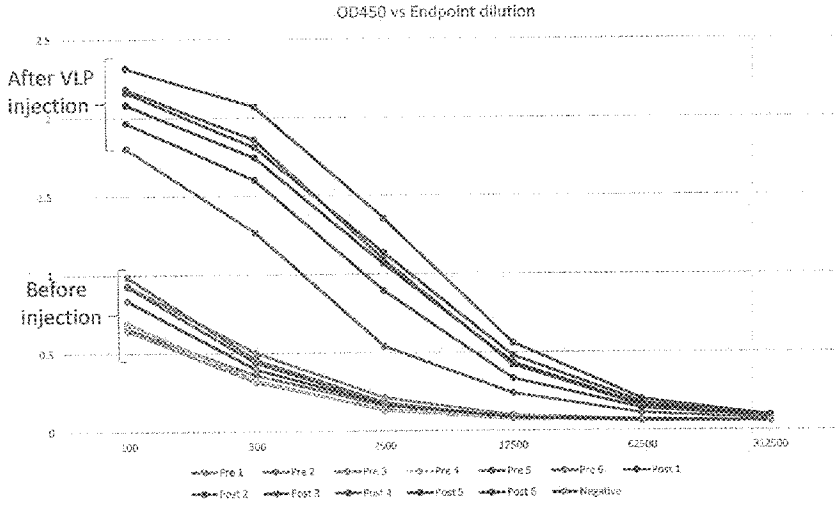


FIG. 10

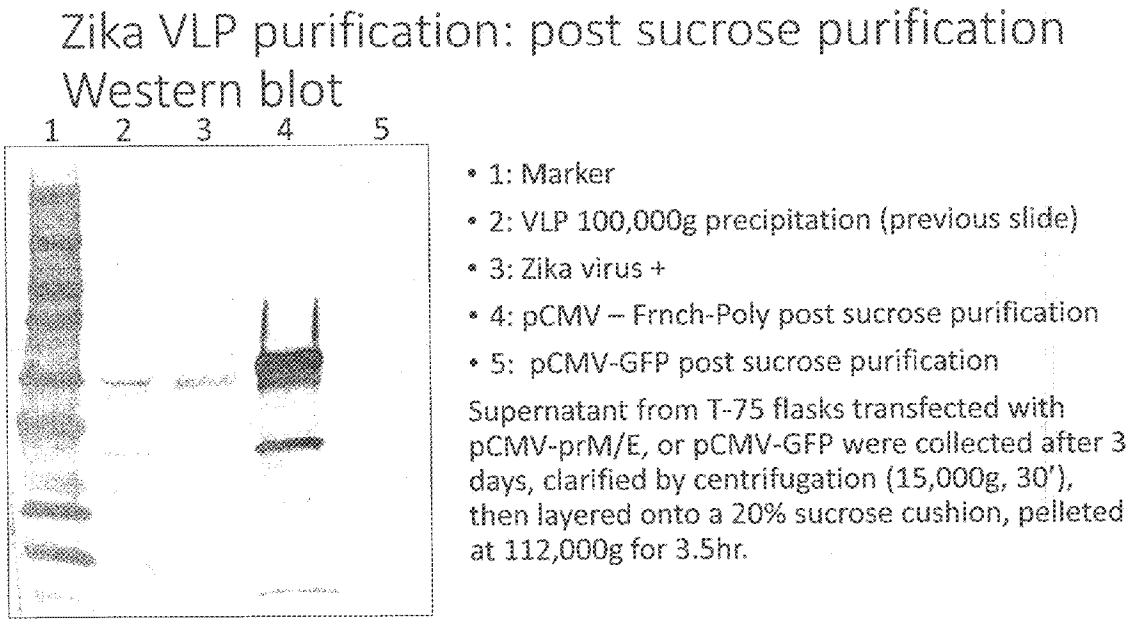

Zika VLP purification: post sucrose purification
Western blot
1 2 3 4 5
• 1: Marker
• 2: VLP 100,000g precipitation (previous slide)
• 3: Zika virus +
• 4: pCMV – Frnch-Poly post sucrose purification
• 5: pCMV-GFP post sucrose purification
Supernatant from T-75 flasks transfected with pCMV-prM/E, or pCMV-GFP were collected after 3 days, clarified by centrifugation (15,000g, 30'), then layered onto a 20% sucrose cushion, pelleted at 112,000g for 3.5hr.

FIG. 11

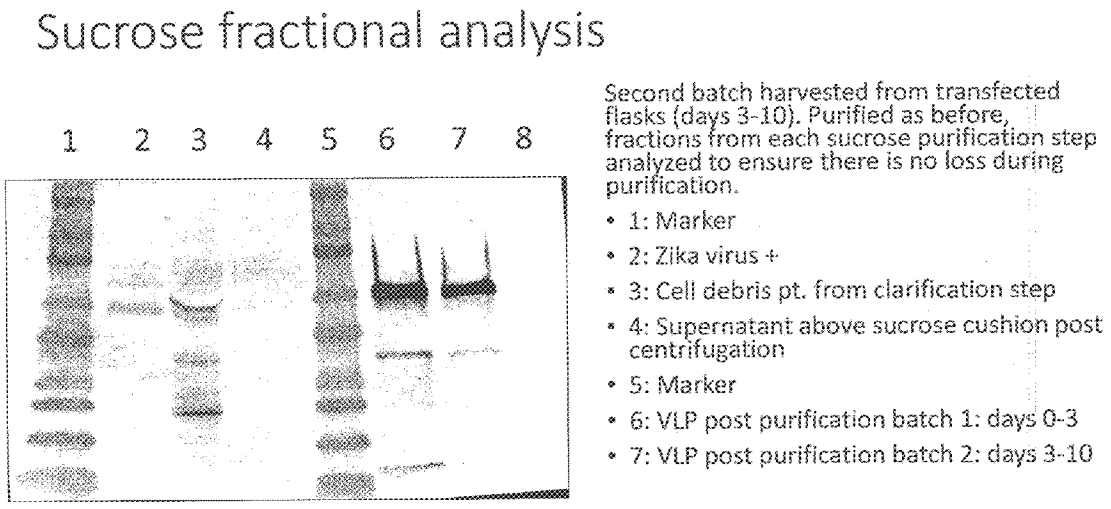

Sucrose fractional analysis
1 2 3 4 5 6 7 8
Second batch harvested from transfected flasks (days 3-10). Purified as before, fractions from each sucrose purification step analyzed to ensure there is no loss during purification.
• 1: Marker
• 2: Zika virus +
• 3: Cell debris pt. from clarification step
• 4: Supernatant above sucrose cushion post centrifugation
• 5: Marker
• 6: VLP post purification batch 1: days 0-3
• 7: VLP post purification batch 2: days 3-10

FIG. 12

pCMV expressed much more protein than pTriex

- pCMV-Col. and all pTriex constructs didn't express significant levels of VLPs

more protein from the second batch of VLPs (days 3-10) about 60ug total from about 100ml

productivity of the cells was highest in the first three days, yielding ~50ug per 15ml = 3.3ug per ml, or 3.3 mg/liter

clone Zeocin resistance gene into pCMV vector for stable cell line

- Generated cell line with pTriex, but terminated after western data

FIG. 13

Mouse study

- **Mice**: 11 AG129 mixed sex, age
- **Route of vaccinations**: IM
- **Adjuvant**: 1mg Alum
- **Route of challenge: ID footpad**
- **Challenge Dose:** 1e2 PFU

Grp	Construct	Rt	Sex	Age weeks	Dose	N=
1	VLP+ adjuvant	IM	F (n=2) M (n=3)	12 (n=5)	2 ug total protein	5
2	Adjuvant	IM	F (n=1) M (n=3)	12 (n=3) 9 (n=3)	N/A	6

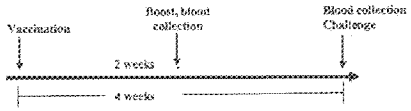


FIG. 14

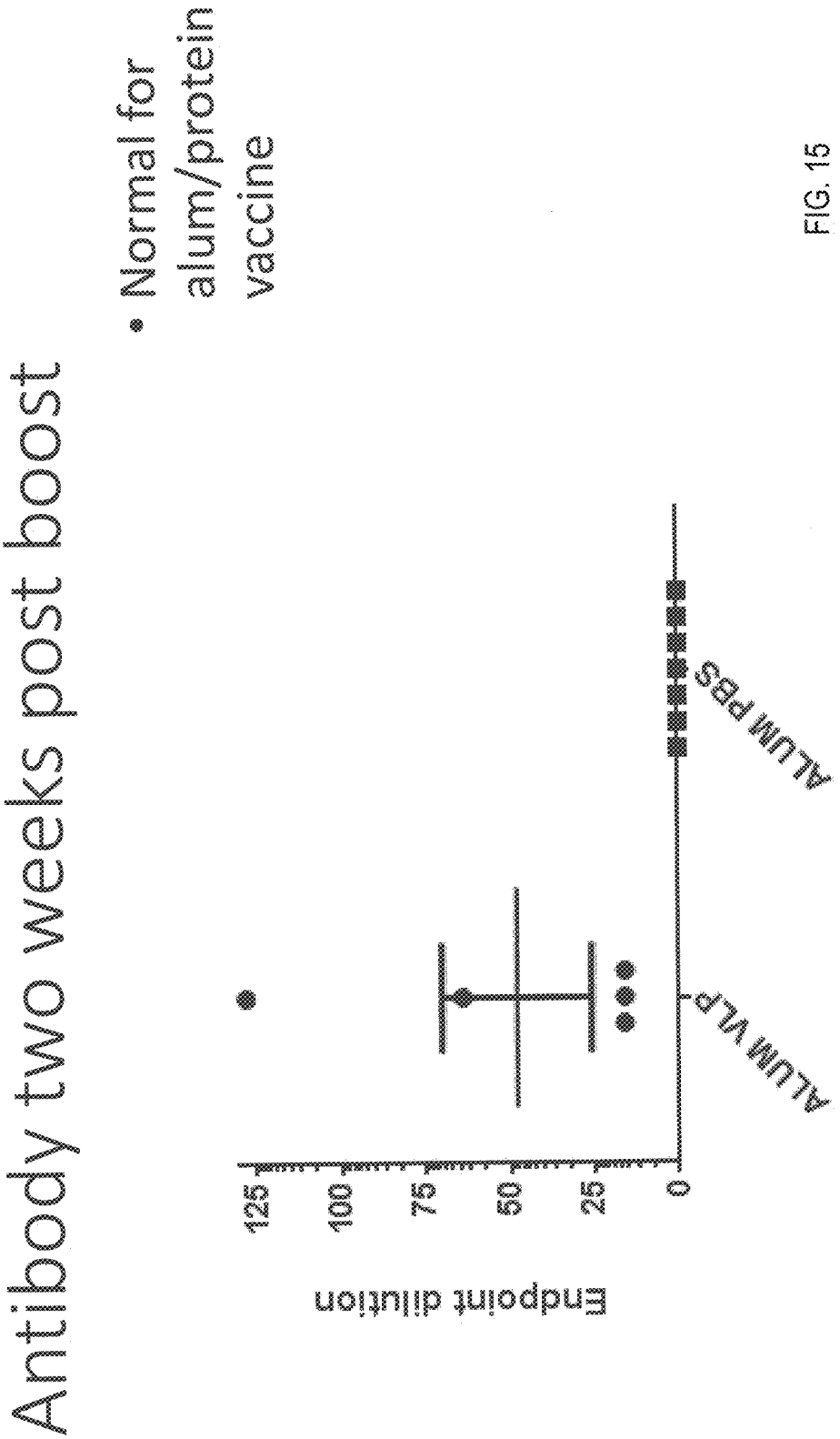

Antibody two weeks post boost
• Normal for alum/protein vaccine
Endpoint dilution
125
100
75
50
25
0
ALUM VLP
ALUM PBS

FIG. 15

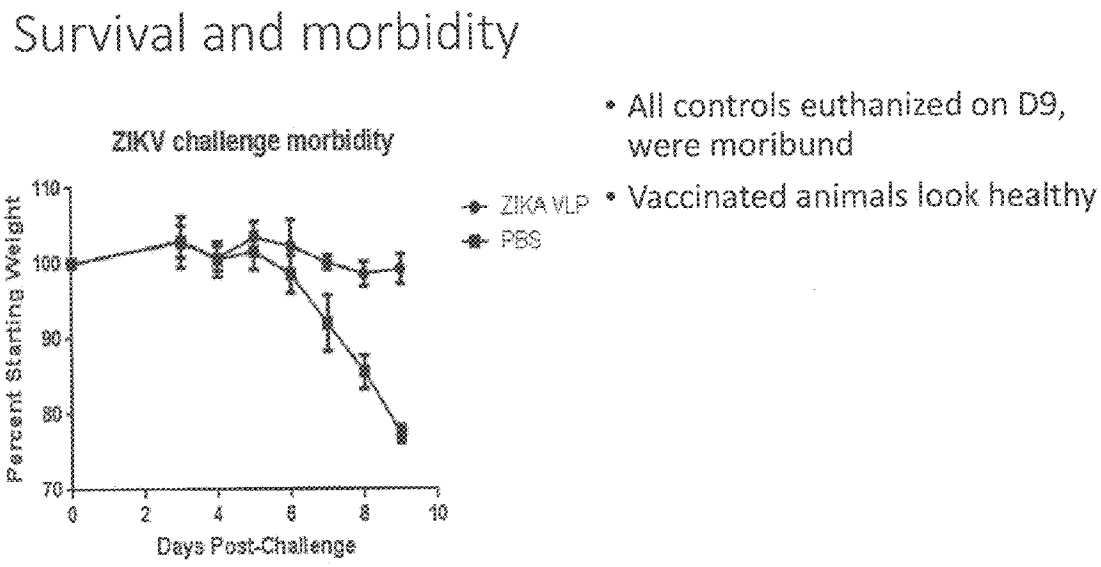

Survival and morbidity
ZIKV challenge morbidity
Percent Starting Weight
110
100
90
80
70
0
2
4
6
8
10
Days Post-Challenge
ZIKA VLP
PBS
• All controls euthanized on D9, were moribund
• Vaccinated animals look healthy

FIG. 16

FIG. 17A.

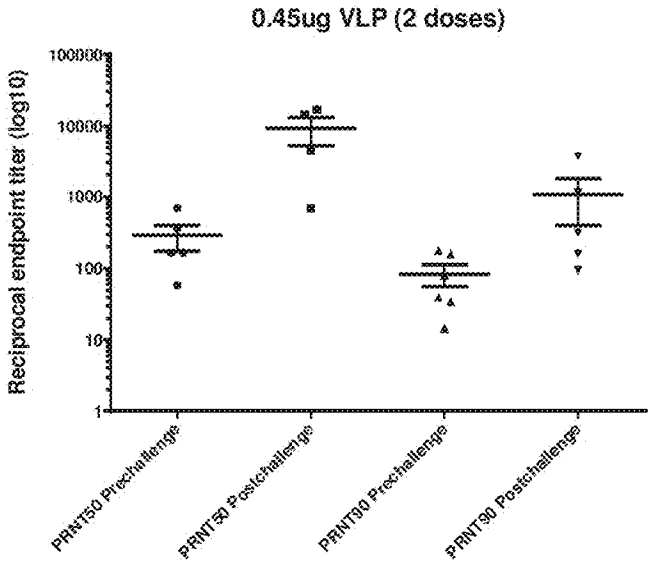


FIG. 17B.

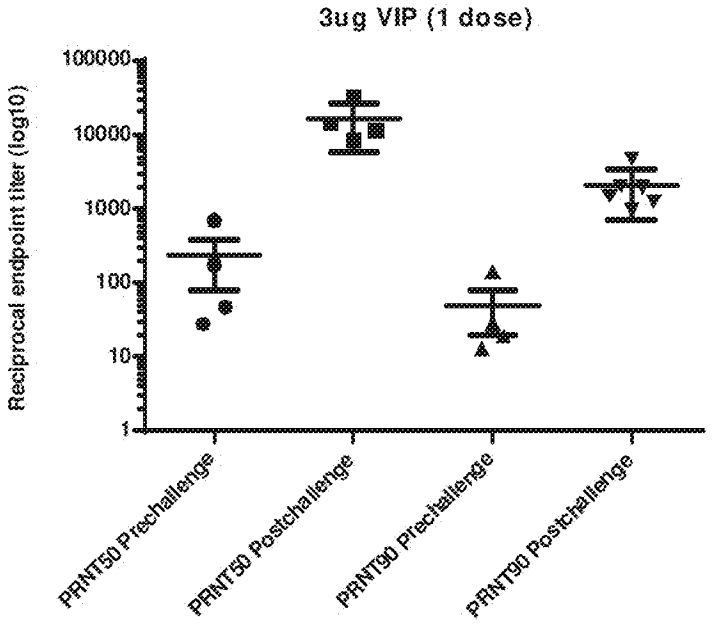


FIG. 17C

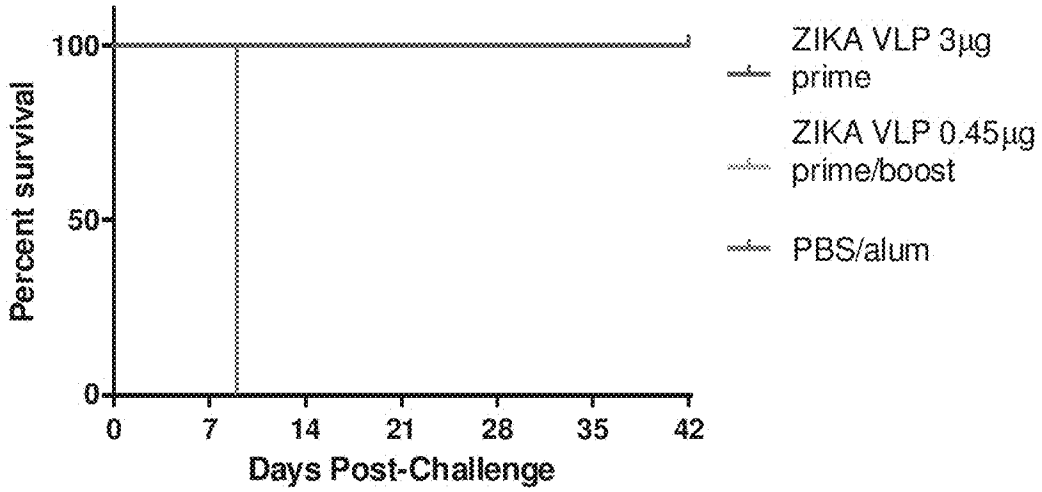

Percent survival
100
50
0
0
7
14
21
28
35
42
Days Post-Challenge
ZIKA VLP 3µg prime
ZIKA VLP 0.45µg prime/boost
PBS/alum

FIG. 18A.

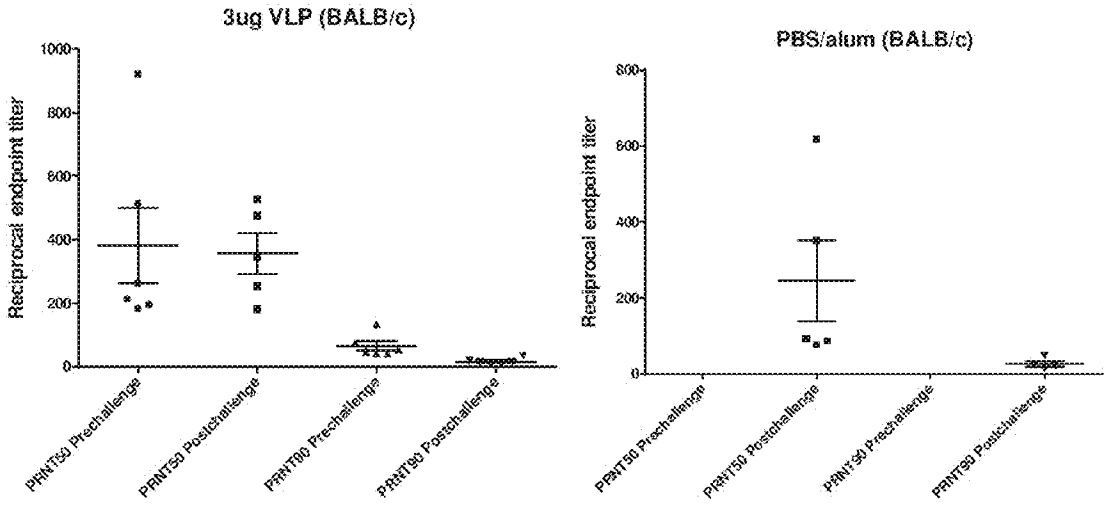


FIG. 18B.

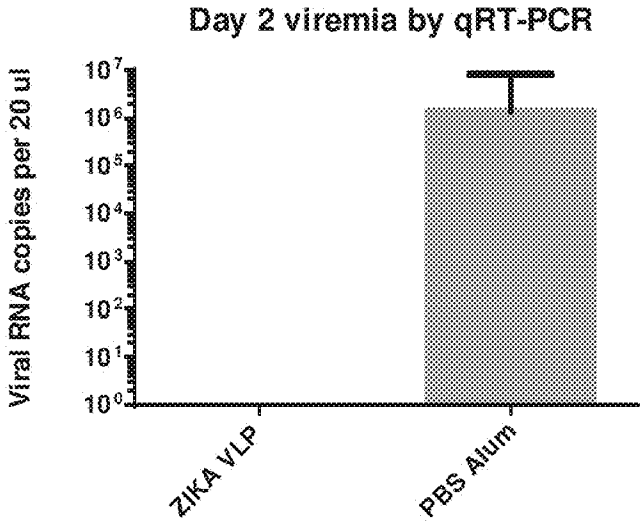
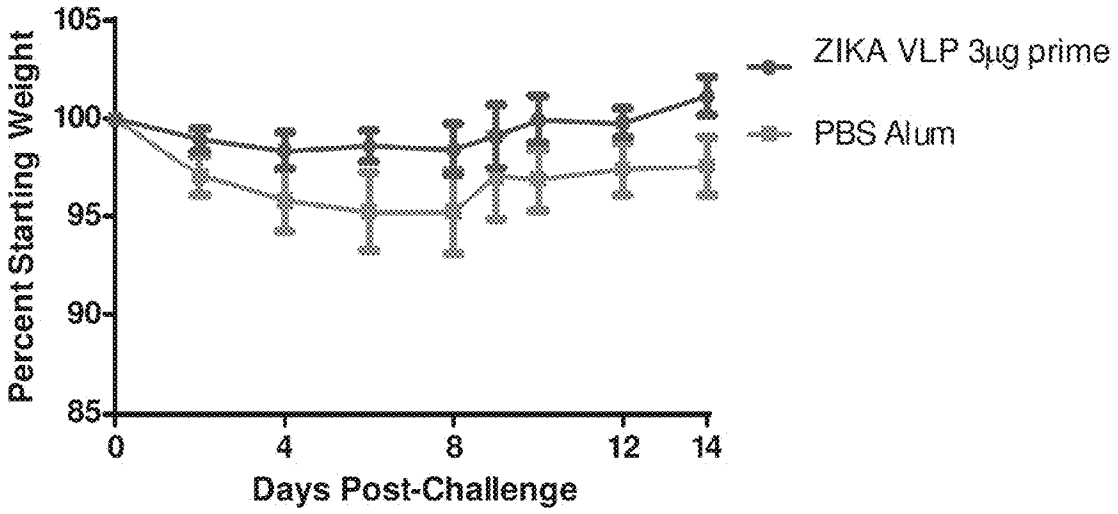


FIG. 18C.


105
100
95
90
85
Percent Starting Weight
0
4
8
12
14
Days Post-Challenge
ZIKA VLP 3μg prime
PBS Alum

ZIKA VIRUS VACCINES USING VIRUS-LIKE PARTICLES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of the filing date of U.S. application Ser. No. 62/352,904, filed on Jun. 21, 2016, and U.S. application Ser. No. 62/384,967, filed on Sep. 8, 2016, the disclosure of which are incorpraoted by reference herein.

BACKGROUND

[0002] Zika virus (ZIKV; Flaviviridae, Flavivirus) is an emerging arbovirus, transmitted by *Aedes* mosquitoes (loos et al., 2014). ZIKV has a positive-sense, single-stranded RNA genome, approximately 11 kilobases in length that encodes three structural proteins: the capsid (C), premembrane/membrane (prM), and envelope (E), and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, 2K, NS4B, and NS5). Based on a genetic study using nucleotide sequences derived from the NS5 gene, there are three ZIKV lineages: East African, West African, and Asian (Musso, 2015; Faye et al., 2014). ZIKV emerged out of Africa and previously caused outbreaks of febrile disease in the Yap islands of the Federated states of Micronesia (Duffy et al., 2009), French Polynesia (Cao-Lormeau et al., 2014), and Oceania. Currently, several Latin American countries are experiencing the first-ever reported local transmission of ZIKV in the Americas (Hennessey et al., 2016). The current outbreak in the Americas is cause for great concern, because of the fast and uncontrolled autochthonous spread. Clinically, infection with ZIKV resembles dengue fever and several other arboviral diseases (Dyer, 2015), but it has been linked to neurological syndromes and congenital malformation (Pinto Junior et al., 2015). Alarmingly, the rate of microcephaly (small head, reduced brain size, impaired neurocognitive development) in infants born to pregnant women has increased significantly (20-fold in 2015) in areas with high ZIKV incidence in Brazil (Oliveira Melo et al., 2016) (Butler, 2016). In February 2016, the World Health Organization declared the Zika virus an international public health emergency, prompted by its link to microcephaly. As many as four million people could be infected by the end of the year (Galland, 2016).

[0003] To date, there are no vaccines or antiviral therapy for ZIKV, although successful vaccines have been developed for other flavivirus infections (dengue, Japanese encephalitis and yellow fever).

SUMMARY

[0004] Mosquito-borne Zika virus (ZIKV) typically causes a mild and self-limiting illness known as Zika fever, which often is accompanied by maculopapular rash, headache, and myalgia. However, more serious consequences have been reported for ZIKV infection during pregnancy, microcephaly of the fetus. As described herein, Zika virus-like particles (VLPs) were developed and their immunogenicity and protective efficacy were evaluated in a small animal model for wild-type ZIKV. The prM and E genes of ZIKV strain 33 H/PF/2013 with a nascent signal sequence in the 3' coding region of the capsid protein were cloned into a pCMV expression vector under the control of a cytomegalovirus (CMV) promoter and CMV polyadenylation signal. Following transfection of HEK293 cells, ZIKV-VLPs expression was confirmed by Western blot and transmission electron microscopy. ZIKV-VLPs (about 0.45 μg) were formulated with 0.2% Imject alum and used to inject groups of six-week-old AG129 mice by the intramuscular (IM) route, followed by a boost administration two weeks later. Control groups received PBS mixed with alum. At five weeks post-initial vaccination all animals were challenged with 200 PFU (>400 LD50s) of ZIKV strain H/PF/2013 by injection into the right hind footpad. All control animals (n=6) died 9 days post challenge, while vaccinated mice survived with no morbidity or weight loss and had significantly lower viremia. This was in contrast to Dengue VLPs produced from prM and E, which did not produce a protective immune response (Pijlman, 2015). Significant levels of neutralizing antibodies were observed in all ZIKV-VLP vaccinated mice compared to control groups. The role of neutralizing antibodies in protecting mice was demonstrated by antibody passive transfer studies; naive AG129 mice that received pooled serum from VLP vaccinated animals were fully protected. Thus, the present findings demonstrate the protective efficacy of the ZIKV-VLP vaccine and highlight the role that neutralizing antibodies play in protection against ZIKV infection.

[0005] One advantage of VLPs is that VLPs structurally mimic the conformation of native viruses but do not contain any viral genetic material (no viral replication) and are therefore non-infectious. This is in contrast to a live attenuated vaccine (which has genetic material) or in the case of insufficient inactivation of killed vaccines (resulting in viral replication). A VLP vaccine approach eliminates concerns associated with such replication for pregnant women and other populations at high risk for suffering the effects of ZIKV infections.

[0006] In one embodiment, a recombinant nucleic acid vector is provided comprising a heterologous promoter operably linked to a sequence encoding flavivirus, e.g., ZIKV, prM/E. In one embodiment, the vector lacks nucleic acid sequences encoding one or more of flavivirus NS1, NS2A, NS2B, NS3, NS4A, NS4B or NS5 and optionally lacks nucleic acid sequences encoding functional flavivirus capsid, e.g., a protein that aggregates so as to form a viral capsid having a diameter of about 50 to 60 nm or about 45 nm to 70 nm. In one embodiment, the heterologous promoter is expressed in mammalian cells. In one embodiment, the heterologous promoter is a heterologous viral promoter. In one embodiment, the heterologous promoter comprises a CMV promoter, a SV40 promoter, an EF-1α promoter or a PGK1 promoter. In one embodiment, the flavivirus is a Zika virus. In one embodiment, the vector sequences are from a Zika virus from the East African or West African lineage. In one embodiment, only a portion of flavivirus capsid sequences is included, e.g., a C-terminal portion of a flavivirus capsid that is linked to prM/E sequences as in the poly-protein that is expressed by wild-type flavivirus. In one embodiment, the portion of the capsid sequence includes amino acids 98 to 112 of the capsid protein encoded by SEQ ID NO:1 or a protein having at least 80%, 82%, 85%, 87%, 90%, 92%, 95%, 97%, 99% or more amino acid sequence identity thereto. In one embodiment, the prM/E sequences have at least 80% %, 82%, 85%, 87%, 90%, 92%, 95%, 97%, 98%, 99% or more amino acid sequence identity to the prM/E sequences encoded by any one of SEQ ID Nos. 1-3, 5 or 11-13. In one embodiment, the portion of the capsid

sequence lacks a NS2B-3 cleavage site, e.g., KEKKRR (SEQ ID NO:10). In one embodiment, the prM/E sequences are operably linked to a heterologous secretion signal. In one embodiment, the vector further comprises an intron and/or enhancer sequence, e.g., 5' to a prM/E coding sequence. In one embodiment, the vector further comprises comprises an intron, internal ribosome entry sequence, or an enhancer sequence, or any combinantion thereof.

[0007] A recombinant host cell comprising the vector is also provided. In one embodiment, the cell is a mammalian, e.g., Vero cell, HeLa cell or CHO cell, insect or yeast cell. In one embodiment, the cell is a human or simian cell. In one embodiment, the genome of the cell is augmented, e.g., stably augmented, with nucleic acid sequences encoding flavivirus NS2B, e.g., the source of NS2B may be heterologous or homologous to the source for prM/E. In one embodiment, the genome of the cell is augmented, e.g., stably augmented, with nucleic acid sequences encoding flavivirus capsid, e.g., the capsid may be heterologous or homologous to prM/E, which sequences are optionally integrated into the genome of the cell. In one embodiment, the genome of the cell is augmented with nucleic acid sequences encding flavivuirus NS2B, which sequences are optionally integrated into the genome of the cell. In one embodiment, the vector is integrated into the genome of the host cell.

[0008] Also provided is a method to prepare flavivirus VLPs. The method includes contacting a culture of isolated host cells that do not express one or more of flavivirus NS1, NS2A, NS2B, NS3, NS4A, NS4B or NS5 and optionally do not express functional flavivirus capsid, with the recombinant vector and collecting VLPs from supernatant of the culture. Thus, in one embodiment, the isolated host cells do not have flavivirus sequences prior to contact with the vector. In one embodiment, the collected particles have a diameter of about 10 to 100 nm, e.g., 20 to 60 nm, 40 to 70 nm or 40 to 60 nm. In one embodiment, the host cell expresses flavivirus NS2B. In one embodiment, the host cell expresses flavivirus capsid protein and optionally NS2B.

[0009] Further provided is a preparation comprising a flavivirus VLPs. The VLP comprises a lipid bilayer comprising flavivinis prM/E but lacks one or more of a flavivirus NS1, NS2A, NS2B, NS3, NS4A, NS4B or NS5 and optionally lacks functional flavivirus capsid. Such a preparation may be used in a vaccine or immunogenic composition. The vaccine or immunogenic composition may have about 10 μg to 1000 μg, e.g., 200 μg to 400 μg or 400 μg to 800 μg, about 0.5 μg to 100 μg, about 1 μg to 50 μg, about 5 μg to 75 μg, about 1 to 500 mg, e.g., about 20 to 50 mg, about 100 to 300 or about 300 to 400 mg, of VLP. The vaccine or immunogenic composition may further comprise one or more adjuvants. In one embodiment, the adjuvant comprises alum, monophosphoryl lipid A (MPLA), squalene, a TLR4 agonist, dimethyldioctadecylammonium, tripalmitoyl-S-glyceryl cysteine, trehalose dibehenate; saponin, MF59, AS03, virosomes, ASO4, CpG, imidazoquinoline, poly I:C, flagellin, or any combination thereof In one embodiment, an adjuvant is included at about 0.001 mg to about 10 mg, about 0.01 to about 10 mg, about 1 to about 20 mg, or about 10 mg to about 100 mg.

[0010] Further provided is a method to prevent, inhibit or treat flavivirus infection in a mammal. The method includes administering an effective amount of the recombinant vector, a host cell having the vector or the vaccine or immunogenic composition having the VLPs. In one embodiment, the mammal is a female mammal. In one embodiment, the vector, host cell, vaccine or immunogenic composition is administered subcutaneously, intradermally, intramuscularly or intravenously to the mammal.

[0011] In one embodiment, a method to passively prevent, inhibit or treat flavivirus infection in a mammal is provided. The method includes obtaining serum or plasma having anti-flavivirus antibodies from a mammal exposed to flavivinis and optionally isolating antibodies from the serum or plasma; and administering an effective amount of the serum or plasma, or isolated antibodies, to a different mammal at risk of or having a flavivirus infection. In one embodiment, the mammal is immunocompromised. In one embodiment, the anti-flavivirus antibodies are isolated from the serum before administration. In one embodiment, the mammal is a human.

BRIEF DESCRIPTION OF THE FIGURES

[0012] FIGS. **1**A-E. In vitro characterization of Zika virus like particles. A) Schematic of pCMV-prM/E expression cassette. B) Western blot analysis of Zika virus like particles. Lanes are, 1) Bio-rad precision plus kaleidoscope protein standards. 2): pCMV-prM/E transfection pre sucrose cushion purification supe. 3) 3.5×10^4 PFU ZIKV positive control. 4) pCMV-prM/E transfection post sucrose cushion purification pt. 5) pCMV-GFP transfection post sucrose cushion purification pt. C-E) Sucrose cushion purified Zika VLPs observed using transmission electron microscopy. C) VLPs stained with Tungsten. Diameter is indicated. Background protein staining also apparent. D) VLP stained with Tungsten. Membrane proteins visible on the surface of VLP are indicated with arrow. Background protein staining apparent. E) VLP stained with Uranyl acetate. Membrane proteins visible on the surface of VLP are indicated with an arrow.

[0013] FIGS. **2**A-F. Protection of ZIKVLPS in AG129 mice. A) Neutralizing antibody titers (+/−SD) of vaccinated AG129 mice pre boost and pre challenge. B) Average weight loss (+/−SD) of AG129 after ID challenge with 200 PFU ZIKV over a 14 day period. C) Survival of 11 week old AG129 after ID challenge with 200 PFU ZIKV over a 14 day period. D) Viremia (+/−SD) in serum samples from mice two days post challenge by qRT-PCR. Values are total RNA copies per reaction. E) Viremia (+/−SD) in serum samples from mice two days post challenge by $TCID_{50}$. F) $PRNT_{50}$ and $PRNT_{90}$ values (+/−SD) of serum samples taken from ZIKVLP vaccinated AG129 mice post challenge, and pre challenge serum from PBS/alum mice.

[0014] FIGS. **3**A-B. ZIKVLP serum transfer to naïve AG129 mice. A) Average weight loss (+/−SD) of 8 week AG129 transferred serum from mice vaccinated with ZIKVLPs after ID challenge with 20 PFU of ZIKV over a 14 day period. B) Survival of AG129 after challenge with ZIKV over a 14 day period.

[0015] FIG. **4**. LD50 of ZIKV in AG129 mice. Survival of AG129 after ZIKV over a 14 day period.

[0016] FIG. **5**A-B. A) Weight loss of AG129 after ID challenge with 20 PFU ZIKV over a 12 day period. B) Survival of AG129 after ID challenge with 200 PFU ZIKV over a 12 day period.

[0017] FIGS. **6**A-B. Sequence of a vector with an exemplary coding sequence to express prM/E (SEQ ID NO:5).

[0018] FIG. **7**. Schematic of a pCMV (A) and pTriex4-neo (B) vector for expression of prM/E.

[0019] FIG. **8**A-C. Images showing GFP expression in HEK293 cells. A) pTri px4-neo GFP expression, B) pCMV GFP expression, and C) pCMV GFP expression.

[0020] FIG. **9**. Western blot analysis of pTriex versus pCMV prM/E expression. Lane 1: Zika virus +; lanes 3,9: pCMV-GFP cells (pt.) and supernatant (sup.); lanes 4,10: pCMV-Columbia pt., sup.; lanes 5,11: pCMV-French-Poly pt., sup.; lanes 6, 12: pTriex-Columbia pt., sup.; and lanes 7, 13: pTriex-French-Poly pt., sup.

[0021] FIG. **10**. Anti-Zika antibodies in mice before and after VLP exposure. Mice were injected IP with about 10^6 $TCID_{50}$ of ZIKV. 5 weeks later the mice were bled, then injected with crude VLP supernatant. Mice were bled 7 days after injection and antibodies analyzed by ZIKV ELISA.

[0022] FIG. **11**. Western blot of sucrose purified VLPs. Lane 1: marker; lane 2: VLP 100,000 g precipitation; lane 3: Zika virus +; lane 4: pCMV—French-Poly post sucrose purification; and lane 5: pCMV-GFP post sucrose purification. Cells in T-75 flasks were transfected with pCMV-prM/E, or pCMV-GFP, and supernatants were collected after 3 days, then clarified by centrifugation (15,000 g, 30 minutes), then layered onto a 20% sucrose cushion, and pelleted at 112,000 g for 3.5 hours.

[0023] FIG. **12**. Sucrose fractional analysis. Lane 1: marker; lane 2: Zika virus +; lane 3: Cell debris (pt.) from clarification step; lane 4: Supernatant above sucrose cushion post centrifugation; lane 5: marker; lane 6: VLP post purification batch 1: days 0-3; and lane 7: VLP post purification batch 2: days 3-10. A second batch was harvested from transfected flasks (days 3-10). Purified as before, fractions from each sucrose purification step were analyzed to ensure there was no loss during purification.

[0024] FIG. **13**. Comparison of protein expression for VLPs produced from pCMV and pTriex constructs.

[0025] FIG. **14**. Mouse study. 11 AG129 mice of mixed sex and age were used. VLPs were administered IM along with 1 mg Alum. Challenge virus (100 PFU) was administered ID.

[0026] FIG. **15**. Antibody levels two weeks post boost.

[0027] FIG. **16**. Survival and morbidity. All controls were moribund on day 9.

[0028] FIGS. **17**A-C. Dose response of ZIKVLPS in AG129 mice. A-B) $PRNT_{50}$ and $PRNT_{90}$ values (+/−SD) of serum samples taken from AG129 mice administered a prime and boost of 0.45 μg (A) or a prime only of 3.0 μg (B) ZIKVLPs pre and post challenge. C) Survival of 11 week old AG129 after ID challenge with 200 PFU ZIKV over a 14 day period.

[0029] FIGS. **18**A-C. Protection of ZIKVLPS in BALB/c mice. A) $PRNT_{50}$ and $PRNT_{90}$ values (+/−SD) of serum samples taken from BALB/c mice administered a prime only of 3.0 μg ZIKVLPs post challenge. B) Viremia (+/−SD) in serum samples from mice two days post challenge by qRT-PCR. Values are total RNA copies per reaction. C) Average weight loss (+/−SD) of BALB/c mice after ID challenge with 200 PFU ZIKV over a 14 day period.

DETAILED DESCRIPTION

Definitions

[0030] As used herein, the terms "isolated" refers to in vitro preparation, isolation of a nucleic acid molecule such as a vector or plasmid of the invention or a virus-like particle of the invention, so that it is not associated with in vivo substances, or is substantially purified from in vitro substances. An isolated virus-like particle preparation is generally obtained by in vitro culture and propagation and is substantially free from infectious agents. As used herein, "substantially free" means below the level of detection for a particular infectious agent using standard detection methods for that agent. As used herein, the term "recombinant nucleic acid" or "recombinant DNA sequence or segment" refers to a nucleic acid, e.g., to DNA, that has been derived or isolated from a source, that may be subsequently chemically altered in vitro, so that its sequence is not naturally occurring, or corresponds to naturally occurring sequences that are not positioned as they would be positioned in the native genome. An example of DNA "derived" from a source, would be a DNA sequence that is identified as a useful fragment, and which is then chemically synthesized in essentially pure form. An example of such DNA "isolated" from a source would be a useful DNA sequence that is excised or removed from said source by chemical means, e.g., by the use of restriction endonucleases, so that it can be further manipulated, e.g., amplified, for use in the invention, by the methodology of genetic engineering.

[0031] A signal peptide (sometimes referred to as signal sequence, secretory signal, e.g., an Oikosin 15 secretory signal, targeting signal, localization signal, localization sequence, transit peptide, leader sequence or leader peptide) is a short (about 5 to 30 amino acids long) peptide present at the N-terminus of proteins that are destined towards the secretory pathway. These proteins include those that reside either inside certain organelles (the endoplasmic reticulum, golgi or endosomes), secreted from the cell, or inserted into most cellular membranes. Although most type I membrane-bound proteins have signal peptides, the majority of type II and multi-spanning membrane-bound proteins are targeted to the secretory pathway by their first transmembrane domain, which biochemically resembles a signal sequence except that it is not cleaved. Signal sequences generally have a tripartite structure, consisting of a hydrophobic care region (h-region) flanked by an n- and c-region. The latter contains the signal peptidase (SPase) consensus cleavage site. Usually, signal sequences are cleaved off co-translationally, the resulting cleaved signal sequences are termed signal peptides.

Exemplary Embodiments

[0032] Zika virus infection transmitted by *Aedes* mosquitoes is now receiving considerable attention due to its associated with microcephaly and Guillain-Barre syndrome. According to the CDC, there have been over 500 cases of travel-related Zika infections in America to date, with no locally-acquired vector-borne cases reported; in contrast, over 700 cases have been reported in US territories, of which nearly all were locally-transmitted.

[0033] Computational analysis has identified ZIKV envelope glycoproteins as a good candidate for vaccine development, as these are the most immunogenic (Shawan, 2015). Several approaches are currently being explored to develop a ZIKV vaccine, including inactivated, recombinant live-attenuated viruses, protein subunit vaccines, or DNA vaccines. A VLP vaccine approach against ZIKV may eliminate concerns of live attenuated vaccines and insufficient inactivation of killed vaccines for pregnant women and other populations at high risk of suffering the devastating effects of ZIKV infections.

[0034] VLPs are structurally mimic the conformation of native virions but do not generate progeny viruses (VLPs are "non-infectious") and do not contain any viral genetic material. VLPs are known to be highly immunogenic and elicit higher titer neutralizing antibody responses than subunit vaccines based on individual proteins (Wang et al., 2013). Such VLPs present viral spikes and other surface components that display linear or conformational epitopes in a repetitive array that effectively results in recognition by B-cells (Metz and Pijlman, 2016). This recognition leads to B cell signaling and MHC class II up-regulation that facilitates the generation of high titer specific antibodies. VLPs from viruses, including hepatitis B virus, West Nile virus and Chikungunya virus, elicit high titer neutralizing antibody responses that contribute to protective immunity in preclinical animal models and in humans (Akahata et al., 2010; Spohn et al., 2010; Wang et al., 2012).

[0035] As mentioned above, a VLP vaccine approach against ZIKV eliminates concerns of live attenuated vaccines and insufficient inactivation of killed vaccines for pregnant women and other populations at high risk of suffering the devastating effects of ZIKV infections. The generation of ZIKV-VLPs containing the prM and E genes as well as the immunogenicity and efficacy testing in the AG129 mouse model is described herein. A position in the secretory signal was identified that likely allows for higher than normal levels of VLP secretion, due to the absence of an auto (NS2b-3) cleavage signal. Using bioinformatic signal sequence prediction tools, the putative signal sequences of ZIKV starting from positions aa 98-aa 112 were examined, and a site was selected that putatively resulted in the highest secretion score. The prM and E genes from ZIKV (Colombian isolate; GenBank accession no. KU646827) were combined with a secretory signal (positions aa 98-aa 112), were cloned into a mammalian expression vector (pCMV-prM/E). HEK-293 cells were transfected and supernatants were harvested from the cells at approximately 10 days post transfection. Transfected HEK-293 cells secreted VLPs with relatively high yields, likely due to the inclusion of a secretory signal that allows for higher than normal levels of VLP secretion. The cell supernatants contained a fraction of extracellular particles that were purified by ultracentrifugation though a sucrose cushion. These particles reacted with known ZIKV antibodies by Western Blot. Western blot analysis also revealed relatively high yields of VLPs after purification, indicating the potential for scalable production. To test the efficacy of this VLP vaccine, AG129 mice susceptible to ZIKV were vacinated with 2 μg of total protein (about 400-500 ng of VLPs) formulated with 1 mg of adjuvant, and the mice boosted with the same vaccine two weeks later. At two weeks post boost, serum from vaccinated animals was collected and tested for anti-ZIKV neutralizing antibodies. Three weeks post boost mice were challenged with 200 PFU of ZIKV (about 400 LD_{50}s). All control animals (n=6) died by 9 days post challenge, while vaccinated mice survived with no morbidity/illness (as of 11 days post-challenge). Passive transfer of antibodies from vaccinated mice was efficacious in protecting susceptible mice from Zika infections. Thus, the present findings show the protective efficacy of a ZIKV-VLP vaccine and highlight the important role that neutralizing antibodies play in protection against ZIKV infection. Further, passive transfer may be employed as a treatment for immune-compromised patients that cannot receive a vaccine.

[0036] In one embodiment, a recombinant nucleic acid vector is provided comprising a heterologous promoter operably linked to a sequence encoding ZIKV, prM/E. In one embodiment, the vector lacks nucleic acid sequences encoding ZIKV NS1, NS2A, NS2B, NS3, NS4A, NS4B or NS5 and optionally lacks nucleic acid sequences encoding functional ZIKV capsid, e.g., a protein that aggregates so as to form a viral capsid having a diameter of about 50 to 60 nm. In one embodiment, the heterologous promoter is expressed in mammalian cells. In one embodiment, the heterologous promoter is a heterologous viral promoter. In one embodiment, only a portion of ZIKV capsid sequences is included, e.g., a C-terminal portion of a ZIKV capsid that is linked to prM/E sequences as in the polyprotein that is expressed by wild-type flavivirus. In one embodiment, the portion of the capsid sequence includes amino acids 98 to 112 of the capsid protein encoded by SEQ ID NO:1 or a protein having at least 80%, 82%, 85%, 87%, 90%, 92%, 95%, 97%, 99% or more amino acid sequence identity thereto. In one embodiment, the prM/E sequences have at least 80% %, 82%, 85%, 87%, 90%, 92%, 95%, 97%, 99% or more amino acid sequence identity to the prM/E sequences encoded by any one of SEQ ID Nos. 1-3 or 5. In one embodiment, the portion of the capsid sequence lacks a NS2B-3 cleavage site. In one embodiment, the prM/E sequences are operably linked to a heterologous secretion signal. In one embodiment, the vector further comprises an intron and/or enhancer sequence, e.g., 5' to a prM/E coding sequence.

[0037] A recombinant host cell comprising the vector is also provided. In one embodiment, the cell is a mammalian cell. In one embodiment, the cell is a human or simian cell. In one embodiment, the genome of the cell is augmented, e.g., stably augmented, with nucleic acid sequences encoding ZIKV NS2B, e.g., the source of NS2B may be heterologous or homologous to the source for prM/E. In one embodiment, the genome of the cell is augmented, e.g., stably augmented, with nucleic acid sequences encoding ZIKV capsid, e.g., the capsid may be heterologous or homologous to prM/E. In one embodiment, the vector is integrated into the genome of the host cell.

[0038] Also provided is a method to prepare ZIKV VLPs. The method includes contacting a culture of isolated host cells that do not express ZIKV NS1, NS2A, NS2B, NS3, NS4A, NS4B or NS5 and optionally do not express functional ZIKV capsid, with the recombinant vector and collecting VLPs from supernatant of the culture. Thus, in one embodiment, the isolated host cells do not have ZIKV sequences prior to contact with the vector. In one embodiment, the collected particles have a diameter of about 10 to 100 nm, e.g., 20 to 60 nm, 40 to 70 nm or 40 to 60 nm. In one embodiment, the host cell expresses ZIKV NS2B. In one embodiment, the host cell expresses ZIKV capsid protein and optionally NS2B.

[0039] Further provided is a preparation comprising a ZIKV VLPs. The VLP comprises a lipid bilayer comprising ZIKV prM/E but lacks ZIKV NS1, NS2A, NS2B, NS3, NS4A, NS4B or NS5 and optionally lacks functional ZIKV capsid. Such a preparation may be used in a vaccine or immunogenic composition. The vaccine or immunogenic composition may have about 10 to 1000 μg, e.g., 200 to 400 μg or 400 to 800 μg, or about 1 to about 500 mg, e.g., about 20 to 50 mg, about 100 to 300 or about 300 to 400 mg, of VLP. The vaccine or immunogenic composition may further comprise one or more adjuvants. In one embodiment, an

adjuvant is included at about 0.01 to about 10 mg, about 1 to about 20 mg, or about 10 mg to about 100 mg.

[0040] Further provided is a method to prevent, inhibit or treat ZIKV infection in a mammal. The method includes administering an effective amount of the recombinant vector, a host cell having the vector or the vaccine or immunogenic composition having the VLPs. In one embodiment, the mammal is a female mammal. In one embodiment, the vector, host cell, vaccine or immunogenic composition is administered intradermally, intramuscularly or intravenously to the mammal.

[0041] In one embodiment, a method to passively prevent, inhibit or treat ZIKV infection in a mammal is provided. The method includes obtaining serum or plasma having anti-ZIKV antibodies from a mammal exposed to ZIKV and optionally isolating antibodies from the serum or plasma; and administering an effective amount of the serum or plasma, or isolated antibodies, to a different mammal at risk of or having a ZIKV infection. In one embodiment, the mammal is immunocompromised. In one embodiment, the anti-flavivirus antibodies are isolated from the serum before administration. In one embodiment, the mammal is a human.

Exemplary Adjuvants

[0042] Adjuvants are compounds that enhance the specific immune response against co-inoculated antigens. Adjuvants can be used for various purposes: to enhance the immunogenicity of highly purified or recombinant antigens; to reduce the amount of antigen or the number of immunizations needed for protective immunity; to prime the efficacy of vaccines in newborns, the elderly or immuno-compromised persons; or as antigen delivery systems for the uptake of antigens by the mucosa. Ideally, adjuvants should not induce immune responses against themselves and promote an appropriate immune response (i.e., cellular or antibody immunity depending on requirements for protection). Adjuvants can be classified into three groups: active immunostimulants, being substances that increase the immune response to the antigen; carriers being immunogenic proteins that provide T-cell help; and vehicle adjuvants, being oil emulsions or liposomes that serve as a matrix for antigens as well as stimulating the immune response.

[0043] Adjuvant groups include but are not limited to mineral salt adjuvants, e.g., alum-based adjuvants and salts of calcium, iron and zirconium; tensoactive adjuvants, e.g, Quil A which is a saponin derived from an aqueous extract from the bark of *Quillaja saponaria:* Saponins induce a strong adjuvant effect to T-dependent as well as T-independent antigens. Other adjuvant groups are bacteria-derived substances including cell wall peptidoglycan or lipopolysaccharide of Gram-negative bacteria, that enhance immune response against co-administered antigens and which is mediated through activation of Toll-like receptors; lipopolysaccharides (LPS) which are potent B-cell mitogens, but also activate T cells; and trehalose dimycolate (TCM), which simulates both humoral and cellular responses.

[0044] Other adjuvants are emulsions, e.g., oil in water or water in oil emulsions such as FIA (Freund's incomplete adjuvant), Montanide, Adjuvant 65, and Lipovant; liposomes, which may enhance both humoral and cellular immunity; polymeric adjuvants such as biocompatible and biodegradable microspheres; cytokines; carbohydrates; inulin-derived adjuvants, e.g., gamma inulin, a carbohydrate derived from plant roots of the Compositae family, is a potent humoral and cellular immune adjuvant and algammulin, which is a combination of γ-inulin and aluminium hydroxide. Other carbohydrate adjuvants include polysaccharides based on glucose and mannose including but not limited to glucans, dextrans, lentinans, glucomannans, galactomannans, levans and xylans.

[0045] Some well known parenteral adjuvants, like MDP, monophosphoryl lipid A (MPL) and LPS, also act as mucosal adjuvants. Other mucosal adjuvants poly(DL-lactide-coglycolide) (DL-PLG), cellulose acetate, iminocarbonates, proteinoid microspheres, polyanhydrides, dextrans, as well as particles produced from natural materials like alginates, geletine and plant seeds.

[0046] Adjuvants for DNA immunizations include different cytokines, polylactic microspheres, polycarbonates and polystyrene particles.

[0047] In one embodiment, adjuvants useful in the vaccines, compositions and methods described herein include, but are not limited to, mineral salts such as aluminum salts, calcium salts, iron salts, and circonium slats, saponin, e.g., Quid A including QS21, squalene (e.g., AS03), TLR ligands, bacterial MDP (N-acetyl muramyl-L-alanyl-D-isoglutamine), lipopolysaccharide (LPS), Lipid A, montanide, Adjuvant 65, Lipovant, Incomplete Freund's adjuvant (IFA), liposmes, microparticles formed of, for example, poly(D,L-lactide (coglycolide)), cytokines, e.g., IFN-gamma or GMCSF, or carbohydrates such as gamma inulin, glucans, dextrans, lentinans, glucomannans and/or glactomannans.

Pharmaceutical Compositions

[0048] Pharmaceutical compositions of the present invention, suitable for inoculation or for parenteral or oral administration, comprise flavivirus VLPs, optionally further comprising sterile aqueous or non-aqueous solutions, suspensions, and emulsions. The compositions can further comprise auxiliary agents or excipients, as known in the art. See, e.g., Berkow et al., 1987; *Avery's Drug Treatment,* 1987. The composition of the invention is generally presented in the form of individual doses (unit doses).

[0049] Vaccines may contain about 0.1 to 500 ng, 0.1 to 500 μg, or 1 to 100 μg, of VLPs. In one embodiment, the vaccine may contain about 100 μg to about 500 μg of VLPs. In one embodiment, the vaccine may contain about at least 100 ng of VLPs. In one embodiment, the vaccine may contain about at least 500 ng of VLPs. In one embodiment, the vaccine may contain about at least 1000 ng of VLPs. In one embodiment, the vaccine may contain about at least 50 μg of VLPs. In one embodiment, the vaccine may contain less than about 750 μg of VLPs. In one embodiment, the vaccine may contain less than about 250 μg of VLPs. In one embodiment, the vaccine may contain less than about 100 μg of VLPs. In one embodiment, the vaccine may contain less than about 40 μg of VLPs. The vaccine forming the main constituent of the vaccine composition of the invention may comprise a combination of different flavirus VLPs, for example, at least two of the three types, Chinese, West African or East African.

[0050] Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and/or emulsions, which may contain auxiliary agents or excipients known in the art. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Carriers or occlusive dressings can be used to increase skin

permeability and enhance antigen absorption. Liquid dosage forms for oral administration may generally comprise a liposome solution containing the liquid dosage form. Suitable forms for suspending liposomes include emulsions, suspensions, solutions, syrups, and elixirs containing inert diluents commonly used in the art, such as purified water. Besides the inert diluents, such compositions can also include adjuvants, wetting agents, emulsifying and suspending agents, or sweetening, flavoring, or perfuming agents. See, e.g., Avery's, 1987.

[0051] When a composition of the present invention is used for administration to an individual, it can further comprise salts, buffers, adjuvants, or other substances which are desirable for improving the efficacy of the composition. For vaccines, adjuvants, substances which can augment a specific immune response, can be used. Normally, the adjuvant and the composition are mixed prior to presentation to the immune system, or presented separately, but into the same site of the organism being immunized. Examples of materials suitable for use in vaccine compositions are provided.

[0052] A pharmaceutical composition according to the present invention may further or additionally comprise at least one chemotherapeutic compound, for example, immunosuppressants, anti-inflammatory agents or immune enhancers, chemotherapeutics including, but not limited to, gamma globulin, amantadine, guanidine, hydroxybenzimidazole, interferon-α, interferon-β, interferon-γ, tumor necrosis factor-alpha, thiosemicarbarzones, methisazone, rifampin, ribavirin, a pyrimidine analog, a purine analog, foscarnet, phosphonoacetic acid, acyclovir, dideoxynucleosides, a protease inhibitor, or ganciclovir.

[0053] The composition can also contain variable but small quantities of endotoxin-free formaldehyde, and preservatives, which have been found safe and not contributing to undesirable effects in the organism to which the composition is administered.

Pharmaceutical Purposes

[0054] The administration of the composition (or the antisera that it elicits) may be for either a "prophylactic" or "therapeutic" purpose. When provided prophylactically, the compositions of the invention which are vaccines, are provided before any symptom of a pathogen infection becomes manifest. The prophylactic administration of the composition serves to prevent or attenuate any subsequent infection or one or more symptoms associated with the disease.

[0055] When provided therapeutically, a VLP vaccine is provided upon the detection of a symptom of actual infection. The therapeutic administration of the vaccine serves to attenuate any actual infection. See, e.g., Avery, 1987.

[0056] Thus, a VLP vaccine composition of the present invention may thus be provided either before the onset of infection (so as to prevent or attenuate an anticipated infection) or after the initiation of an actual infection.

[0057] A composition is said to be "pharmacologically acceptable" if its administration can be tolerated by a recipient patient. Such an agent is said to be administered in a "therapeutically effective amount" if the amount administered is physiologically significant. A composition of the present invention is physiologically significant if its presence results in a detectable change in the physiology of a recipient patient, e.g., enhances at least one primary or secondary humoral or cellular immune response against at least one strain of an infectious flavivirus.

[0058] The "protection" provided need not be absolute, i.e., the flavivirus infection need not be totally prevented or eradicated, if there is a statistically significant improvement compared with a control population or set of patients. Protection may be limited to mitigating the severity or rapidity of onset of symptoms of the flavivirus infection.

Pharmaceutical Administration

[0059] A composition of the present invention may confer resistance to one or more pathogens, e.g., one or more flavivirus strains, by either passive immunization or active immunization. In active immunization, an inactivated or attenuated live vaccine composition is administered prophylactically to a host (e.g., a mammal), and the host's immune response to the administration protects against infection and/or disease. For passive immunization, the elicited antisera can be recovered and administered to a recipient suspected of having an infection caused by at least one flavivirus strain.

[0060] In one embodiment, the vaccine or immune serum is provided to a mammalian female (at or prior to pregnancy or parturition), under conditions of time and amount sufficient to cause the production of an immune response which serves to protect both the female and the fetus or newborn (via passive incorporation of the antibodies across the placenta or in the mother's milk).

[0061] The present invention thus includes methods for preventing or attenuating a disorder or disease, e.g., an infection. As used herein, a vaccine is said to prevent or attenuate an infection if its administration results either in the total or partial attenuation (i.e., suppression) of a symptom or condition of the infection, or in the total or partial immunity of the individual to the disease.

[0062] At least one VLP or composition thereof, of the present invention may be administered by any means that achieve the intended purposes, using a pharmaceutical composition as previously described.

[0063] For example, administration of such a composition may be by various parenteral routes such as subcutaneous, intravenous, intradermal, intramuscular, intraperitoneal, intranasal, oral or transdermal routes. Parenteral administration can be by bolus injection or by gradual perfusion over time. One mode of using a pharmaceutical composition of the present invention is by intramuscular or subcutaneous application. See, e.g., Avery, 1987.

[0064] A typical regimen for preventing, suppressing, or treating a flavivirus related pathology, comprises administration of an effective amount of a vaccine composition as described herein, administered as a single treatment, or repeated as enhancing or booster dosages, over a period up to and including between one week and about 24 months, or any range or value therein.

[0065] According to the present invention, an "effective amount" of a composition is one that is sufficient to achieve a desired biological effect. It is understood that the effective dosage will be dependent upon the age, sex, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect wanted. The ranges of effective doses provided below are not intended to limit the invention and represent suggested dose ranges. However, the dosage will be tailored to the indi-

vidual subject, as is understood and determinable by one of skill in the art. See, e.g., Avery's, 1987; and Ebadi, 1985.

[0066] The invention will be further described by the following non-limiting examples.

EXAMPLE 1

Experimental Procedures

Cells and Viruses

[0067] African Green Monkey kidney cells (Vero) and Human embryonic kidney 293 (HEK293) were obtained from ATCC (ATCC; Manassas, Va., USA) and grown in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS; Hyclone, Logan, Utah), 2 mM L-glutamine, 1.5 g/L sodium bicarbonate, 100 U/mL of penicillin, 100 μg/mL of streptomycin, and incubated at 37° C. in 5% CO_2. ZIKV strain H/PF/2013 (GenBank: KJ776791), was obtained from Xavier de Lamballerie (European Virus Archive, Marseille France). Virus stocks were prepared by inoculation onto a confluent monolayer of Vero cells.

Animals

[0068] Mice of the 129/Sv background deficient in alpha/beta interferon (IFN-α/β) and IFN-Y receptors (AG129 mice) were obtained from B&K Universal Limited (Hull, England) and were bred in the pathogen-free animal facilities of the University of Wisconsin-Madison School of Veterinary Medicine. Groups of mixed sex mice were used for all experiments.

Production and purification of ZIKV VLPs

[0069] The prM and E genes of ZIKV strain H/PF/2013 with nascent signal sequence were cloned into a pCM/V expression vector under the control of a cytomegalovirus (CMV) promoter and CMV polyadenylation signal (pCMV-prM/E). Endotoxin free, transfection grade DNA was prepared using Maxiprep kit (Zymo Research, Irvine, Calif.). VLPs were expressed by transfecting 90% confluent monolayers of HEK293 cells in a T-75 flasks with 15 μg of pCMV-prM/E using Fugene HD (Promega, Madison, Wis.) transfection reagent according to manufacturer protocol. The 10 ml supernatant was harvested 72 hours after transfection, and clarified by centrifugation at 15,000 RCF for 30 minutes at 4° C. Clarified supernatants were layered onto a 20% sucrose cushion and ultra-centrifuged in a SW-28 rotor at 112,000 RCF for 3.5 hours at 4° C. Pellet (PT) and supernatant (SUP) fractions at each step were saved for analysis by SDS-PAGE and Western blot. Post sucrose cushion PT were resuspended in Phosphate Buffered Saline (PBS) pH 7.2. Total protein in VLP preparations was quantified by Bradford assay. VLP specific protein was determined by comparing Zika specific bands on SDS-PAGE gels to known concentrations of BSA using ImageJ software.

Western Blot

[0070] VLP fractions were boiled in Laemmli sample buffer (BioRad, Hercules, Calif., USA) and resolved on a 4-20% SDS-PAGE gel (Biorad) by electrophoresis using a Mini-PROTEAN 3 system (BIO-RAD, CA). Gels were electroblotted onto nitrocellulose membranes using a Turboblot® system. Membranes were blocked in 5% (W/V) skim milk and probed with mouse hyper immune ascites fluid primary antibody (1:5000) and goat anti-mouse HRP conjugated secondary antibody (1:5000). Membranes were developed using a solid phase 3,3',5,5'-tetramethylbenzidine (TMB) substrate system.

Transmission Electron Microscopy

[0071] Samples were negatively stained for electron microscopy using the drop method. A drop of sample was placed on a Pioloform™ (Ted Pella, Inc.) carbon-coated 300 Mesh Cu grid, allowed to adsorb for 30 seconds, and the excess removed with filter paper. Next, a drop of methylamine tungstate or uranyl acetate (Nano-W, Nanoprobes Inc.) was placed on the still wet grid, and the excess removed. The negatively stained sample was allowed to dry, and was documented in a Philips CM120 (Eindhoven, The Netherlands) transmission electron microscope at 80 kV. Images were obtained using a SIS MegaView III digital camera (Soft Imaging Systems, Lakewood, Color.).

Vaccination and Viral Challenge

[0072] For VLP formulations, 0.45 μg of sucrose cushion purified VLPs was mixed with 0.2% Imject Alum (Thermo Scientific) according to manufacturer's protocol. Groups of AG129 mice were injected intramuscularly (IM) with VLPs mixed with alum (n=5) or PBS mixed with alum (n=6) at 6 weeks of age, and again at 8 weeks of age. Sub-mandibular blood draws were performed pre boost and pre challenge to collect serum for analysis by neutralization assays and for passive transfer studies.

[0073] Vaccinated mice were challenged with 200 PFU of ZIKV strain H/PF/2013 in 25 μl volumes by intradermal (ID) injection into the right hind footpad. Following infection, mice were monitored daily for the duration of the study. Mice that were moribund or that lost greater than 20% of starting weight were humanely euthanized. Sub-mandibular blood draws were performed on day two post challenge (PC) and serum collected to measure viremia.

[0074] For passive transfer studies, 5 naive mice were injected intraperitoneally (IP) with 500 μl of pooled serum from VLP vaccinated, diluted serum (1:5 n=4, 1:10, n=4), or serum from PBS/alum (n=5) treated mice. At 12 hours post transfer, mice were challenged with 20 PFU in 25 μl as above.

Viremia Assays

[0075] Viremia was determined by TCID50 assay. Briefly, serum was serially diluted ten-fold in microtiter plates 263 and added to duplicate wells of Vero cells in 96-well plates, incubated at 37° C. for 5 days, then fixed and 264 stained with 10% (W/V) crystal violet in 10% (V/V) formalin. Plates were observed under a light microscope to determine the 50% tissue culture infective doses (TCID50s). Serum samples were also tested for viral RNA copies by qRT-PCR. RNA was extracted from 0.02 ml of serum using the ZR Viral 267 RNA Kit (Zymo Research, Irvine, Calif.). Viral RNA was quantified by qRT-PCR using the primers and probe designed by Lanciotti et al. (Lanciotti et al., 2008). The qRT-PCR was performed using the iTaq Universal Probes One-Step Kit (BioRad, Hercules, Calif.) on an iCycler instrument (BioRad, Hercules, Calif.). Primers and probe were used at final concentrations of 500 nM and 250 nM respectively. Cycling conditions were as follows: 50° C. for 10 minutes and 95° C. for 2 minutes, followed by 40

cycles of 95° C. for 15 seconds and 60° C. for 30 seconds. Virus concentration was determined by interpolation onto an internal standard curve made up of a 5-point dilution series of in vitro transcribed RNA.

Neutralization Assay

[0076] Serum antibody titers were deteiliiined by microneutralization assay. Briefly, serum was incubated at 56° C. for 30 minutes to inactivate complement and then serially diluted two-fold in microtiter plates. 200 PFUs of virus were added to each well and incubated at 37° C. for 1 hour. The virus-serum mixture was added to duplicate wells of Vero cells in 96-well plates, incubated at 37° C. for 5 days, then fixed and stained with 10% (W/V) crystal violet in 10% (V/V) formalin, then observed under a light microscope. The titer was determined as the serum dilution resulting in the complete neutralization of the virus.

Plaque Reduction Neutralization Test

[0077] Serum samples were serially diluted, mixed with 200 PFU of the ZIKV H/PF/2013 strain and incubated for 1 hour at 37° C. This serum/virus mixture was added to confluent layers of Vero cells in 96 well plates and incubated for 1 hour at 37° C., after which the serum/virus mixture was removed and overlay solution (3% CMC, 1×DMEM, 2% FBS and 1×Anti/Anti) was added. After 48 hours of infection, the monolayers were fixed with 4% PFA, washed twice with PBS, and then incubated with ZIKV hyperimmune mouse ascitic fluid (1:2000, UTMB) diluted in blocking solution (1×PBS, 0.01% Tween-20 and 5% Milk) and incubated overnight at 4° C. Plates were washed three times with PBS-T and then peroxidase-labeled goat anti-mouse secondary antibody (1:2000) was incubated on monolayers for 2 hours at 37° C. Following incubation, cells were washed a final three times with PBS-T and developed using 3-amino-9-ethylcarbazole (AEC)-peroxidase substrate. The amount of formed foci were counted using an 292 ELISPOT plate reader (ImmunoSPOT-Cellular Technology); quality control was performed to each scanned well to ensure accurate counting. Neutralization percentages (Nx) were calculated per sample/replicate/dilution as follows:

$$Nx = \left\{100 - \left[100\left(\frac{A}{\text{Control}}\right)\right.\right.$$

Where A corresponds to the amount of foci counted in the sample and Control is the geometric mean of foci counted from wells treated with cells and virus only. Data of corresponding transformed dilutions (Log(1/Dilution)) against neutralization percentages per sample was plotted and fitted to a sigmoidal dose-299 response curve to interpolate $PRNT_{50}$ and $PRNT_{90}$ values (GraphPad Prism software).

SEQ ID NO: 9:

mknpkkksgg frivnmlkrg varvspfggl krlpaglllg hgpirmvlai laflrftaik

pslglinrwg svgkkeamei ikkfkkdlaa mlriinarke kkrrgadtsv givgllltta

maaevtrrgs ayymyldrnd ageaisfptt lgmnkcyiqi mdlghmcdat msyecpmlde

gvepddvdcw cnttstwvvy gtchhkkgea rrsrravtlp shstrklqtr sqtwlesrey

tkhlirvenw ifrnpgfala aaaiawllgs stsqkviylv milliapays ircigvsnrd

fvegmsggtw vdvvlehggc vtvmaqdkpt vdielvtttv snmaevrsyc yeasisdmas

dsrcptqgea yldkqsdtqy vckrtlvdrg wgngcglfgk gslvtcakfa cskkmtgksi

qpenleyrim lsvhgsqhsg mivndtghet denrakveit pnspraeatl ggfgslgldc

eprtgldfsd lyyltmnnkh wlvhkewfhd iplpwhagad tgtphwnnke alvefkdaha

krqtvvvlgs qegavhtala galeaemdga kgrlssghlk crlkmdklrl kgvsyslcta

aftftkipae tlhgtvtvev qyagtdgpck vpaqmavdmq tltpvgrlit anpviteste

nskmmleldp pfgdsyivig vgekkithhw hrsgstigka featvrgakr mavlgdtawd

fgsvggalns lgkgihqifg aafkslfggm swfsqiligt llmwlglntk ngsislmcla

lggvliflst avsadvgcsv dfskketrcg tgvfvyndve awrdrykyhp dsprrlaaav

kqawedgicg issvsrmeni mwrsvegeln aileengvql tvvvgsvknp mwrgpqrlpv

pvnelphgwk awgksyfvra aktnnsfvvd gdtlkecplk hrawnsflve dhgfgvfhts

vwlkvredys lecdpavigt avkgkeavhs dlgywiesek ndtwrlkrah liemktcewp

kshtlwtdgi eesdliipks lagplshhnt regyrtqmkg pwhseeleir feecpgtkvh

veetcgtrgp slrsttasgr vieewccrec tmpplsfrak dgcwygmeir prkepesnlv

rsmvtagstd hmdhfslgvl villmvgegl kkrmttkiii stsmavlvam ilggfsmsdl

aklailmgat faemntggdv ahlaliaafk vrpallvsfi franwtpres mllalascll

-continued

qtaisalegd lmvlingfal awlairamvv prtdnitlai laaltplarg tllvawragl

atcggfmlls lkgkgsvkkn lpfvmalglt avrlvdpinv vgllllltrsg krswppsevl

tavglicala ggfakadiem agpmaavgll ivsyvvsgks vdmyieragd itwekdaevt

gnsprldval desgdfslve ddgppmreii lkvvlmticg mnpiaipfaa gawyvyvktg

krsgalwdvp apkevkkget tdgvyrvmtr rllgstqvgv gvmqegvfht mwhvtkgsal

rsgegrldpy wgdvkqdlvs ycgpwkldaa wdghsevqll avppgerarn iqtlpgifkt

kdgdigaval dypagtsgsp ildkcgrvig lygngvvikn gsyvsaitqg rreeetpvec

fepsmlkkkq ltvldlhpga gktrrvlpei vreaiktrlr tvilaptrvv aaemeealrg

lpvrymttav nvthsgteiv dlmchatfts rllqpirvpn ynlyimdeah ftdpssiaar

gyistrvemg eaaaifmtat ppgtrdafpd snspimdtev evperawssg fdwvtdhsgk

tvwfvpsvrn gneiaacltk agkrviqlsr ktfetefqkt khqewdfvvt tdisemganf

kadrvidsrr clkpvildge rvilagpmpv thasaaqrrg rigrnpnkpg deylygggca

etdedhahwl earmlldniy lqdgliasly rpeadkvaai egefklrteq rktfvelmkr

gdlpvwlayq vasagitytd rrwcfdgttn ntimedsvpa evwtrhgekr vlkprwmdar

vcsdhaalks fkefaagkrg aafgvmealg tlpghmterf qeaidnlavl mraetasrpy

kaaaaqlpet letimllgll gtvslgiffv lmrnkgigkm gfgmvtlgas awlmwlseie

pariacvliv vflllvvlip epekqrspqd nqmaiiimva vgllglitan elgwlertks

dlshlmgrre egatigfsmd idlrpasawa iyaalttfit pavqhavtts ynnyslmama

tqagvlfgmg kgmpfyawdf gvpllmigcy sqltpltliv aiillvahvm ylipglqaaa

araaqkrtaa gimknpvvdg ivvtdidtmt idpqvekkmg qvlliavavs sailsrtawg

wgeaqalita atstlwegsp nkywnsstat slcnifrgsy lagasliytv trnaglvkrr

gggtgetlge kwkarlnqms alefysykks gitevcreea rralkdgvat gghavsrgsa

klrwlvergy lqpygkvidl gcgrggwsyy aatirkvqev kgytkggpgh eepmlvqsyg

wnivrlksgv dvfhmaaepc dtllcdiges ssspeveear tlrvlsmvgd wlekrpgafc

ikvlcpytst mmetlerlqr rvggglvrvp lsrnsthemy wvsgaksnti ksvsttsqll

lgrmdgprrp vkyeedvnlg sgtravvsca eapnmkiign rierirseha etwffdenhp

yrtwayhgsy eaptqgsass lingvvrlls kpwdvvtgvt giamtdttpy gqqrvfkekv

dtrvpdpqeg trqvmsmvss wlwkelgkhk rprvctkeef inkvrsnaal gaifeeekew

ktaveavndp rfwalvdker ehhlrgecqs cvynmmgkre kkqgefgkak gsraiwymwl

garflefeal gflnedhwmg rensgggveg lglqrlgyvl eemsripggr myaddtagwd

trisrfdlen ealitnqmek ghralalaii kytyqnkvvk vlrpaekgkt vmdiisrqdq

rgsgqvvtya lntftnlvvq lirnmeaeev lemqdlwllr rsekvtnwlq sngwdrlkrm

avsgddcvvk piddrfahal rflndmgkvr kdtqewkpst gwdnweevpf cshhfnklhl

kdgrsivvpc rhqdeligra rvspgagwsi retaclaksy aqmwqllyfh rrdlrlmana

icssvpvdwv ptgrttwsih gkgewmtted mlvvwnrvwi eendhmedkt pvtkwtdipy

lgkredlwcg slighrprtt waenikntvn mvrriigdee kymdylstqv rylgeegstp

gvl

RESULTS

Expression and Purification of Soluble, Zika VLPs

[0078] To generate Zika VLPs (ZIKVLPs), the prM/E genes with a native signal sequence were cloned into a pCMV expression vector (pCMV-prM/E) (FIG. **1**A), transfected HEK293 cells and harvested supernatants (supe) 3 days post transfection. 78 μg total protein was recovered from post sucrose purification of which 21.6 μg was VLP protein. Western blot analysis of this pCMV-prM/E supe. revealed expression of about 50 kDa size band (FIG. **1**B, lane 2) that corresponded in size to the predicted size of the Zika viurs E gene, and additionally matched positive control Zika virus stocks (FIG. **1**B, lane 3). To test the hypothesis that expression of Zika prM and E genes spontaneously form extracellular particles, supernatants from pCMV-prM/E and pCMV-GFP (negative control) transfected cells were centrifuged on a sucrose cushion (SC) sufficient for pelleting of flavi virus particles from cell culture proteins (Merino-Ramos et al., 2014). pCMV-prM/E SC purified pellet (pt) appeared to contain high levels of E protein, while pCMV-GFP pt. did not, indicating that staining was specific to expression of 100 prM and E genes.

[0079] To determine if the immune reactive extracellular particles were virus like in nature, transmission electron microscopy (TEM) was performed on pCMV-prM/E SC pt. material. TEM revealed flavi virus 103 like particles with a size that ranged from 30-60 nm (data not show), and a typical size of about 50 nm (FIG. **1**C). High magnification images demonstrated surface structures characteristic of flaviral envelope proteins (FIGS. **1**D, E).

Administration of ZIKVLPs is Immunogenic and Protects Highly ZIKV Susceptible α/β/γ Interferon Deficient Mice

[0080] Mice that received ZIKVLPs developed low levels (GMT=1:9.2) of neutralizing antibodies (nAbs) at 109 two weeks post administration, that increased two weeks after boost (GMT=1:32). Five weeks after primary vaccination, all mice were challenged with 200 PFU of ZIKV by the ID route. Mice administered ZIKVLP maintained weight, while mice that received PBS/alum experienced significant weight loss associated morbidity throughout the challenge period.

[0081] All control mice (n=6) died 9 days after ZIKV challenge. Mice administered ZIKVLP survived with no apparent morbidity. Finally, ZIKVLP vaccinated mice had significantly lower levels of viremia on day 2 post challenge than control mice detected by qRT-PCR (p=0.0356) and 116 TCID50 assay (p=0.0493).

ZIKVLPs Elicit Plaque Reducing Neutralizing Antibody Titers in Mice That Can Be Passively Transferred to Naïve Mice.

[0082] The plaque reduction neutralization test (PRNT) assay is widely considered to be the "gold standard" for characterizing and quantifying circulating levels of anti-dengue and other flaviviral neutralizing antibodies (nAb) (Thomas et al., 2009). A PRNT assay was developed for rapidly measuring ZIKV specific neutralizing antibodies. Pooled serum samples collected from mice pre-challenge, as well as individual serum samples collected from mice post-challenge were tested by this PRNT assay. Pre-challenge, pooled serum from mice administered ZIKVLP had a calculated 90% plaque reduction ($PRNT_{90}$) titer of 1:34. The $PRNT_{90}$ titer increased 2 weeks post challenge (GMT=126 662).

[0083] To test the role of anti-ZIKV antibodies in protection against challenge, groups of mice received ZIKVLP 128 antiserum, undiluted (n=5), diluted 1:5 (n=4), or 1:10 (n=4). As a negative control mice (n=5) were transferred serum from mice previously vaccinated with PBS alum.

[0084] Negative control mice rapidly lost weight starting after day 7 and all died day 9 post challenge. Mice that received undiluted serum maintained weight throughout the 12 day period post challenge, and showed no signs of infection. Mice that received diluted anti-ZIKV antibodies were not protected from challenge, although survival and weigh loss were slightly extended relative to negative control mice 134.

DISCUSSION

[0085] Most experts and public health workers agree that a Zika vaccine is urgently needed. In February 2016, the World Health Organization declared that the recent clusters of microcephaly and other neurological disorders in Brazil constitute a public health emergency of international concern. Their recommendations included enhanced surveillance and research, as well as aggressive measures to reduce infection with Zika virus, particularly amongst pregnant women and women of childbearing age. ZIKV is now receiving considerable attention due to its rapid spread in the Americas, and its association with microcephaly (Mlakar et al., 2016) and Guillain-Barre syndrome (Pinto Junior et al., 2015). In our studies, we designed a ZIKV-virus-like particle (VLP) vaccine, demonstrated expression in vitro by western blot and transmission electron microscopy, and tested the protective efficacy and role of antibodies in protection in the AG129 mouse model.

[0086] Although the transfection and purification procedures for this ZIKV-VLP have yet to be optimized, we had an overall calculated yield of 2.2 mg/ml. Similar expression levels have been reported for other flavivirus VLP expression strategies (Pijlman, 2015). Future work will optimize VLP production and purification parameters, which should significantly increase both yield and purity. Stably transfected HEK cells that continuously express VLPs allow for scalable production to meet global demand for a ZIKV vaccine.

[0087] ZIKV-VLPs, formulated with alum, induced detectable neutralizing antibodies and protected animals against lethal challenge (>400 LD50s) with no morbidity or weight loss. Pre-challenge GMT neutralizing titers were 1:32, and pooled pre-challenge serum $PRNT_{90}$ and $PRNT_{50}$ titers were 1:34 and 1:157 respectively. At a relatively low dose of 450 ng, the present results indicate that the ZIKV VLPs are highly immunogenic. Additionally, the antibody titers we obtained are consistent with those reported for other highly immunogenic flavivirus VLP vaccines (Ohtaki et al., 2010; Pijlman, 2015).

[0088] Vaccinated mice challenged with >400 LD50s had low levels of viremia (mean=127, geometric mean=25.4 TCID50/ml) detected after challenge. Copies of RNA ZIKV genomes in serum of mice were significantly higher than levels of viremia. However, the disparity between viral genome copies and viremia has been observed for other flaviviruses including dengue (Bae et al., 2003). Since AG129 mice are highly susceptible to viral challenge, it is

possible that the challenge dose given for the active vaccination study was artificially high. Additionally, methods for challenging mice from infected mosquito bite should be developed to most accurately mimic natural infection. Animal studies can determine if the ZIK VLP vaccine can protect female mice from contracting ZIKV during pregnancy using established models for such studies (Miner et al., 2016). ZIK-VLP vaccines may be tested in a non-human primate translational model which most accurately mimics human infection.

[0089] A VLP vaccine approach against ZIKV has significant advantages over other technologies as it will eliminate concerns of live attenuated vaccines and insufficient inactivation of killed vaccines for pregnant women and other populations at high risk of suffering the devastating effects of ZIKV infections. In recent years, recombinant virus-like particle (VLP)-based vaccine strategies have been frequently used for novel vaccine design. VLPs are known to be highly immunogenic and elicit higher titer neutralizing antibody responses than subunit vaccines based on individual proteins (Ariano et al., 2010).

[0090] The role of neutralizing antibodies in protecting against ZIKV was demonstrated by antibody passive transfer studies as naive AG129 mice receiving pooled serum from VLP vaccinated animals were fully protected. These results are consistent with previous findings that indicate the important role of antibodies in protecting against many mosquito-borne viruses, such as Japanese encephalitis, yellow fever and chikungunya. In this study, full protection was observed when animals received undiluted serum, with no weight loss or other clinical signs observed. While these studies highlight the importance of serum antibodies in ZIKV protection, upcoming studies will determine the minimum antibody titer needed for protection, whether the ZIKV-VLP can elicit CD8+ responses, and the overall role of cellular immunity in protection. It is also important to determine whether anti-ZIKV antibodies elicited by the VLPs play any role in dengue protection or disease enhancement.

[0091] In this study, the AG129 IFN receptor-deficient mouse model was used for evaluation of the ZIKV-VLP. Recently, the suitability of mice deficient in IFN-α/β and -γ receptors as an animal model for ZIKV was demonstrated, as they are highly susceptible to ZIKV infection and disease, developing rapid viremic dissemination in visceral organs and brain and dying 7-8 days post-infection (Aliota et al., 2016). The AG129 mouse model exhibits an intact adaptive immune system, despite the lack of an IFN response, and it has been used extensively to evaluate vaccines and antivirals for DENV (Brewoo et al., 2012; Fuchs et al., 2014; Johnson and Roehrig, 1999; Sarathy et al., 2015).

[0092] In the present study, aluminum hydroxide (commonly known as alum) was used as the adjuvant for the ZIKV-VLP preparations. Since its first use in 1932, vaccines containing aluminum-based adjuvants have been successfully administered in humans demonstrating excellent safety. A variety of adjuvant formulations may, however, be employed with ZIKV VLPs to enhance immunogenic potential including adjuvants that facilitate antigen dose sparing, enhanced immunogenicity, and/or broadened pathogen protection.

[0093] Thus, a VLP based Zika vaccine is described herein that elicits protective antibodies in mice, and is safe, suitable for scalable production, and highly immunogenic. Fast-tracking development of this ZIKV vaccine is a public health priority and is crucial for restoring confidence and security to people who wish to have children or reside in, or visit areas in which ZIKV is endemic.

EXAMPLE 2

Exemplary Zika Virus Polyprotein Sequences:

[0094] Accession No. KU646827 (Which is Incorporated by Reference Herein)

(SEQ ID NO: 6)

IRCIGVSNRDFVEGMSGGTWVDVVLEHGGCVTVIVIAQDKPTVDIE

LVTTTVSNMAEVRSYCYEASISDMASDSRCPTQGEAYLDKQSDTQYVCKRTLVDRGWG

NGCGLFGKGSLVTCAKFACSKKIVITGKSIQPENLEYRIMLSVHGSQHSGMIVNDTGH

ETDENRAKIVEITPNSPRAEATLGGFGSLGLDCEPRTGLDFSDLYYLMINNKHWLVHK

EWTHDIPLPWELNGADTGTPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTALAGA

LEAEMDGAKGRLSSGHLKCRLKMDKLRLKGVSYSLCTAAFTFTKIPAETLHGTVIVEV

QYAGTDGPCKVPAQIVIAVDMQTLTPVGRLITANPVITESTENSKMMLELDPPFGDSY

IVIGVGEKKITHHAVHRSGSTIGKAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGK

GIHQIFGAAFKSLFGGMSWFSQILIGTLLMWLGLNTKNGSISLMCLALGGVLIFLSTA

VSADVGCSVDFSKKETRCGTGVFVYNDVEAIATRDRYKYHPDSPRRLAAAVKQAWEDG

ICGISSVSRMENIMWRSVEGELNAILEENGVQLTVVVGSVKNPMWRGPQRLPVPVNEL

PHGWKAWGKSYFVRAAKTNNSFVVDGDTLKECPLKHRAWNSFLVEDHGFGVFHTSVWL

KVREDYSLECDPANTIGTAVKGKEAVHSDLGYWIESEKNDTWRLKRAHLIEMKTCEWP

-continued

KSHTLWTDGIEESDLIIPKSLAGPLSHHNTREGYRTQMKGPWHSEELEIRFEECPGTK

ATHVEETCGTRGPSLRSTTASGRVIEEWCCRECTMPPLSFWAKDGCWYGMEIRPRKEP

ESNLVRSMVTAGSTDHMDHFSL

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KU955593 (full-length)

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ttggggcgca tggacgggcc caggaggcca gtgaaatatg aggaggatgt gaatctcggc

tctggcacgc gggctgtggt aagctgcgct gaagctccca acatgaagat cattggtaac

cacattgaaa agatccacag tgaacacgcg gaaacgtggt tctttgacaa gaaccaccca

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gacactaagg tgccagatcc ccaagaaaac actcgtcagg ttataagcat gatctcttcc

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aagactgcag tggaagctgt gaacgatcca aggttctggg ctctagtgga caaggaaaga

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aagaaacaag gggaatttgg aaaggccaag agcagccgcg ccatctggta tatgtggcta

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gaggagaacg accacatgga agacaagacc ccagttacga aatggacaga cattccctat

ttgggaaaaa gggaagactt gtggtgtgga tctctcatag ggcacagacc gcgcaccacc

tgggctgaga acattaaaaa cacagtcaac atggtgcgca ggatcatagg tgatgaagaa

aagtacatgg actacctatc cacccaagtt cgctacttgg gtgaagaagg gtctacacct

ggagtgctgt aa

prM/E proteins include those having at least 80%, 82%, 85%, 87%, 90%, 92%, 95%, 97%, 99% or more amino acid sequence identity to the prM/E proteins encoded by SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:11, SEQ ID NO:12, or SEQ ID NO:13.

[0095] Capsid proteins include those having at least 80%, 82%, 85%, 87%, 90%, 92%, 95%, 97%, 99% or more amino acid sequence identity to the proteins encoded by one or more of SEQ ID NO:1 SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:11, SEQ ID NO:12, or SEQ ID NO:13.

[0096] An exemplary intron/enhancer sequences useful in a vector include: atcgcctggagacgccatccacgctgttttgacctccataggaagacaccgggaccgatccagcctccgcggccgggaa cggtgcattggaacgcggattccccgtgccaagagtgactcaccgtccggatctcagcaagcagtatgtactctccag ggtgggcctggcttccccagtcaagactccagggatttgagggacgctgtgggctcttctatacatgtacctttgcttgc ctcaaccctgactatcttccaggtcaggatcccagagtcaggggtctgtattttcctgctggtggctccagttcaggaaca gtaaaccctgctccgaatattgcctctcacatctcgtcaatctccgcgaggactggggaccctgtgacgaac (SEQ ID NO:4), or a nucleotide sequence having at least 80%, 82%, 85%, 87%, 90%, 92%, 95%, 97%, 99% or more nucleotide sequence identity to SEQ ID NO:4.

[0097] An exemplary vector sequence useful to produce VLPs is shown in FIG. **6** (SEQ ID NO:5).

[0098] An exemplary African lineage Zika isolate has the following nucleotide sequence (SEQ ID NO:11 which encodes the protein provided at Accession No. HQ234500 which is incorporated by reference herein):

atgaaaaacc caaagaagaa atccggagga ttccggattg tcaatatgct aaaacgcgga

gtagcccatg taaacccctt gaggggtttg aagaggctgc cggccggact cctgctgggc

catggaccca tcagaatggt tttggcgata ctagccttct tgagattcac agcaatcaag

ccatcactgg gcctcatcaa tagatagggt tccgtgggga agaaggaggc tatggaaata

ataaaaaagt tcaagaaaga tcttgctgcc atgttgagaa taatcaatgc taggaaggag

aggaagagac atggagctaa tgccaacatc ggaatcgtca acctcctgct gactacagtc

atggcagcag agatcactag acgcgggagt gcatactaca tgtacttgga caggagcgat

gctggtaagg ccatttcttt cgttaccaca ctggggatga acaaatgcca tgtgcagatc

atggacctcg ggcatatgtg tgacgccacc atgagttatg agtgccccat gctggacgag

ggagtggagc cagatgacgt cgattgctgg tgcaacacga catcaacttg ggttgtgtac

ggaacctgtc atcataaaaa aggtgaagca cgacaatcca gaagagccgt gacgcttcct

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gctgtagcta ttgcctggct cctgggaagc tcgacgagcc aaaaagtcat atacttggtc

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ttcgtggagg gcatgtcagg tgggacctgg gttgatgttg tcttggaaca tggaggttgt

gtcaccgtga tggcacagga caagccaaca gttgacatag agttggtcac gacaacggtt

agcaacatgg ccgaagtgag atcctactgc tacgaggcat caatatcgga catggcttca

gacagtcact gcccaacaca aagtgaagcc taccttgaca agcaatcaga cactcaatat

gtctataaaa gaacattggt ggacagaggt tgggaaaatg gatgtggact ttttggcaag

gggagcttgg tgacgtgtgc caagtttaca tgctccaaga aaatgacagg gaagagcatc

cagccggaga acttggagta ccggataatg ctatcagtgc atggatccca gcacagtggg

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gacttttcag atctgtatta cctgaccatg aacaataacg attggttggt gcacaaagag

tggtttcatg acatcccatt accttggcat tctggtgcag acactgaaac tccacactgg

aacaacaaag aggcactggt gaagttcaag gacgcccacg ccaaaaggca aactgttgta

gttctgggga gccaagaaga agccgttcac acggctctcg ctggagctct ggaggctgag

atggatggtg cgaagggaag gctatcctca ggccatttga aatgccgcct aaaaatggac

aagcttaggt tgaagggtgt gtcatattcc ctgtgtaccg cagcgttcac attcaccaag

gttccagctg aaacattgca tggaacagtc acaatggagg tgcagtatac agggaaggat

agaccctgca aggtcccagc ccagatggcg atggacatac agaccctgac cccagttgga

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gccgactagg tcccaactgg gagaaccacc tggtcaatcc atagaaaggg aaaatggata

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[0099] An exemplary Asian lineage Zika isolate has the following sequence (SEQ ID NO:12 which encodes the protein provided at Accession No. HQ234499 which is incorporated by reference herein):

ATGAAAAACC CAAAAAAGAA ATCCGGAGGA TTCCGGATTG

TCAATATGCT AAAACGCGGA GTAGCCCGTG TGAGCCCCTT

TGGGGGCTTG AAGAGGCTAC CAGCTGGACT TCTGCTGGGT

CATGGACCCA TCAGGATGGT CTTGGCGATA CTAGCCTTCT

TGAGATTCAC GGCAATCAAG CCATCACTGG GTCTCATCAA

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ATAAAGAAGT TCAAGAAAGA TCTGGCTGCC ATGCTGAGAA

TAATCAATGC TAGGAAGGAG AAGAAGAGAC GTGGCGCAGA

CACCAGTGTC GGAATTGTTG GCCTCCTGCT GACCACAGCC

ATGGCAGTGG AGGTCACCAG ACGTGGGAGT GCATACTATA

TGTACTTAGA CAGAAGCGAT GCTGGGGAGG CCATATCTTT

TCCAACCACA CTGGGGGTGA ATAAGTGTTA CATACAGATC

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CGATTGCTGG TGCAACACGA CATCGACTTG GGTTGTGTAC

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[0100] An exemplary Spodweni virus lineage has the following nucleotide sequence (SEQ ID NO:13 which encodes the protein provided at Accession No. DQ859064, which is incorporated by reference herein:

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gcaatcggcg aaactgaaga atatagagac tacatgagca cacaggtccg ctatggctcg

gaggaagagc caagcgctgg tatgttgtaa

EXAMPLE 3

[0101] Exemplary vectors expressing GFP were transfected into HEK293 cells and expression was assessed (FIGS. **7-8**). prM/E sequences were also expressed from the two vectors in HEK cells and supernatants and cells analyzed 48 hours later (FIG. **9**). Supernatants were concentrated by centrifugation at 100,000 g for 60 minutes. Western blots were analyzed using University of Texas Medical Branch (UTMB) mouse ascites. More VLPs were secreted from pCMV-FP transfected cells (lane 11 in FIG. **9**) than pTriex transfected cells (lane 13). Sucrose purified fractions were subjected to Western blot (FIGS. **10-11**). pCMV-prM/E SC purified pellet (pt) appeared to contain high levels of E protein while pCMV-GFP pt did not, indicating that staining was specific to expression of prM and E genes. In summary, a pCMVvector expressed more protein than a pTriex vector. VLPs collected at days 3-10 provided for about 60 μg total protein from about 100 mL. On day 3 the productivity of the cells was about 50 μg per 15 mL (3.3 μg per mL, or 3.3 mg/L). For stably transfected cells, a marker, e.g., a Zeocin resistance gene, may be introduced into the vector that expresses prM/E.

[0102] ZIKV VLPS (ZIKVLPs) formulated with alum were injected into 6-8-week-old interferon deficient A129 and AG129 mice. Control mice received PBS/alum. Animals were challenged with 200 PFU (>400 LD_{50}s) of ZIKV strain H/PF/2013. All vaccinated mice survived with no morbidity or weight loss while control animals either died at 9 days post challenge (AG129) or had increased viremia (A129). Neutralizing antibodies were observed in all ZIKVLP vaccinated mice.

EXAMPLE 4

Materials and Methods

Cells and Viruses

[0103] African Green Monkey kidney cells (Vero) and Human embryonic kidney 293 (HEK293) were obtained from ATCC (ATCC; Manassas, Va., USA) and grown in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS; Hyclone, Logan, Utah), 2 mM L-glutamine, 1.5 g/l sodium bicarbonate, 100 U/ml of penicillin, 100 μg/ml of streptomycin, and incubated at 37° C. in 5% CO2. ZIKV strain H/PF/2013 (GenBank: KJ776791), was obtained from Xavier de Lamballerie (European Virus Archive, Marseille France). Virus stocks were prepared by inoculation onto a confluent monolayer of Vero cells.

Animals

[0104] Mice of the 129/Sv background deficient in alpha/beta interferon alpha/beta/gamma (IFN-α/β/IFN-Y) receptors (AG129 mice) were obtained from B&K Universal Limited (Hull, England) and were bred in the pathogen-free animal facilities of the University of Wisconsin-Madison School of Veterinary Medicine. 5-week-old BALB/c mice (The Jackson Laboratory, Maine, USA) were used for wild-type vaccination studies. Groups of mixed sex mice were used for all experiments.

Production and Purification of ZIKV VLPs

[0105] The prM and E genes of ZIKV strain H/PF/2013 with nascent signal sequence were cloned into a pCMV expression vector under the control of a cytomegalovirus (CMV) promoter and CMV polyadenylation signal (pCMV-prM/E, FIG. **1**). Endotoxin free, transfection grade DNA was prepared using Maxiprep kit (Zymo Research, Irvine, Calif.). VLPs were expressed by transfecting 90% confluent monolayers of HEK293 cells in a T-75 flasks with 15 μg of pCMV-prM/E using Fugene HD (Promega, Madison, Wis.) transfection reagent according to manufacturer protocol. The 10 ml supernatant was harvested 72 hr after transfection, and clarified by centrifugation at 15,000 RCF for 30 min at 4° C. Clarified supernatants were layered onto a 20% sucrose cushion and ultra-centrifuged in a SW-28 rotor at 112,000 RCF for 3.5 hours at 4° C. Pellet (PT) and supernatant (SUP.) fractions at each step were saved for analysis by SDS-PAGE and Western blot. Post sucrose cushion PT were resuspended in Phosphate Buffered Saline (PBS) pH 7.2. Total protein in VLP preparations was quantified by Bradford assay. VLP specific protein was determined by comparing Zika specific bands on SDS-PAGE gels to known concentrations of BSA using ImageJ software.

Western Blot

[0106] VLP fractions were boiled in Laemmli sample buffer (BioRad, Hercules, Calif., USA) and resolved on a 4-20% SDS-PAGE gel (Biorad) by electrophoresis using a Mini-PROTEAN 3 system (BIO-RAD, CA). Gels were electroblotted onto nitrocellulose membranes using a Turboblot® system. Membranes were blocked in 5% (W/V) skim milk and probed with mouse hyper immune ascites fluid primary antibody (1:5000) and goat anti-mouse HRP conjugated secondary antibody (1:5000). Membranes were developed using a solid phase 3,3',5,5'-tetramethylbenzidine (TMB) substrate system.

Transmission Electron Microscopy

[0107] Samples were negatively stained for electron microscopy using the drop method. A drop of sample was placed on a Pioloform™ (Ted Pella, Inc.) carbon-coated 300 Mesh Cu grid, allowed to adsorb for 30 seconds, and the excess removed with filter paper. Next, a drop of methylamine tungstate or uranyl acetate (Nano-W, Nanoprobes Inc.) was placed on the still wet grid, and the excess removed. The negatively stained sample was allowed to dry, and was documented in a Philips CM120 (Eindhoven, The Netherlands) transmission electron microscope at 80 kV. Images were obtained using a SIS MegaView III digital camera (Soft Imaging Systems, Lakewood. Colo.).

Vaccination and Viral Challenge

[0108] Each of the following animal studies was performed as one biological replicate. For VLP formulations, the indicated dose of sucrose cushion purified VLPs was mixed with 0.2% Imject Alum (Thermo Scientific) according to manufacturer's protocol. Groups of AG129 mice were injected intramuscularly (TM) with VLPs mixed with alum (n=5) or PBS mixed with alum (n=6) at 6 weeks of age, and again at 8 weeks of age. Sub-mandibular blood draws were

performed pre boost and pre challenge to collect serum for analysis by neutralization assays and for passive transfer studies.

AG129 mice were challenged with 200 PFU of ZIKV strain H/PF/2013 in 25 μL volumes by intraderml (ID) injection into the right hind footpad at 11 weeks of age. Balb/c mice were vaccinated once at 5 weeks of age as above, and challenged at 13 weeks of age with 200 PFU of H/PF/2013 in 50 μl by retro orbital injection (IV route).

[0109] Following infection, mice were monitored daily for the duration of the study. Mice that were moribund or that lost greater than 20% of starting weight were humanely euthanized. Sub-mandibular blood draws were performed on day two post challenge (PC) and serum collected to measure viremia.

[0110] Eight week old AG129 mice were used for passive transfer studies Five naive mice were injected intraperitoneally (IP) with 500 μL of pooled serum from VLP vaccinated, diluted serum (1:5 n=4, 1:10, n=4), or serum from PBS/alum (n=5) treated mice. At 12 h post transfer, mice were challenged with 20 PFU in 25 μl as above.

Viremia Assays

[0111] Viremia was determined by $TCID_{50}$ assay. Briefly, serum was serially diluted ten-fold in microtiter plates and added to duplicate wells of Vero cells in 96-well plates, incubated at 37° C. for 5 days, then fixed and stained with 10% (W/V) crystal violet in 10% (V/V) formalin. Plates were observed under a light microscope to determine the 50% tissue culture infective doses ($TCID_{50}$s). Serum samples were also tested for viral RNA copies by qRT-PCR. RNA was extracted from 0.02ml of serum using the ZR Viral RNA Kit (Zymo Research, Irvine, Calif.). Viral RNA was quantified by qRT-PCR using the primers and probe designed by Lanciotti et al (Lanciotti et al., 2008). The qRT-PCR was performed using the iTaq Universal Probes One-Step Kit (BioRad, Hercules, Calif.) on an iCycler instrument (BioRad, Hercules, Calif.). Primers and probe were used at final concentrations of 500 nM and 250 nM respectively. Cycling conditions were as follows: 50° C. for 10 min and 95° C. for 2 min, followed by 40 cycles of 95° C. for 15 sec and 60° C. for 30 sec. Virus concentration was deteif lined by interpolation onto an internal standard curve made up of a 5-point dilution series of in vitro transcribed RNA, with the lowest copies per reaction being 100.

Neutralization Assay

[0112] Serum antibody titers were determined by microneutralization assay. Briefly, serum was incubated at 56° C. for 30 min to inactivate complement and then serially diluted two-fold in microtiter plates. 200 PFUs of vines were added to each well and incubated at 37° C. for 1 h. The virus-serum mixture was added to duplicate wells of Vero cells in 96-well plates, incubated at 37° C. for 5 days, then fixed and stained with 10% (W/V) crystal violet in 10% (V/V) formalin, then observed under a light microscope. The titer was determined as the serum dilution resulting in the complete neutralization of the virus.

Plaque Reduction Neutralization Test

[0113] Serum samples were serially diluted, mixed with 200 PFU of the ZIKV H/PF/2013 strain and incubated for 1 hr at 37° C. This serum/virus mixture was added to confluent layers of Vero cells in 96 well plates and incubated for 1 hr at 37° C., after which the serum/virus mixture was removed and overlay solution (3% CMC, 1×DMEM, 2% FBS and 1×Anti/Anti) was added. After 48 hrs of infection, the monolayers were fixed with 4% PFA, washed twice with PBS, and then incubated with ZIKV hyperimmune mouse ascitic fluid (1:2000, UTMB) diluted in blocking solution (1×PBS, 0.01% Tween-20 and 5% Milk) and incubated overnight at 4° C. Plates were washed three times with PBS-T and then peroxidase-labeled goat anti-mouse secondary antibody (1:2000) was incubated on monolayers for 2 hours at 37° C. Following incubation, cells were washed a final three times with PBS-T and developed using 3-amino-9-ethylcarbazole (AEC)-peroxidase substrate. The amount of formed foci were counted using an ELISPOT plate reader (ImmunoSPOT-Cellular Technology); quality control was performed to each scanned well to ensure accurate counting. Neutralization percentages (Nx) were calculated per sample/replicate/dilution as follows:

$$Nx = \left\{100 - \left[100\left(\frac{A}{\text{Control}}\right)\right.\right.$$

Where A corresponds to the amount of foci counted in the sample and Control is the geometric mean of foci counted from wells treated with cells and virus only. Data of corresponding transformed dilutions (Log(1/Dilution)) against neutralization percentages per sample was plotted and fitted to a sigmoidal dose-response curve to interpolate $PRNT_{50}$ and $PRNT_{90}$ values (GraphPad Prism software).

RESULTS

[0114] Expression and Purification of Soluble, Zika VLPs To generate Zika VLPs (ZIKVLPs), we cloned the prM/E genes with native signal sequence into a pCMV expression vector (pCMV-prM/E) (FIG. **1**A), transfected HEK293 cells and harvested supernatants (supe.) 3 days post transfection. 78 μg total protein was recovered from post sucrose purification of which 21.6 μg was ZIKVLP protein. Western blot analysis of this pCMV-prM/E supe. revealed expression of an about 50 kDa size band (FIG. **1**B, lane 2) that corresponded in size to the predicted size of the Zika virus E gene, and additionally matched positive control Zika virus stocks (FIG. **1**B, lane 3). To test the hypothesis that expression of Zika prM and E genes spontaneously form extracellular particles, supernatants from pCMV-prM/E and pCMV-GFP (negative control) transfected cells were centrifuged on a sucrose cushion (SC) sufficient for pelleting of flavi virus particles from cell culture proteins (Merino-Ramos et al., 2014). pCMV-prM/E SC purified pellet (pt.) appeared to contain high levels of E protein, indicating that staining was specific to expression of prM and E genes. To determine if the immune reactive extracellular particles were virus like in nature, we performed transmission electron microscopy (TEM) on pCMV-prM/E SC pt. material. TEM revealed virus like particles with a size that ranged from 30-60 nm, and a typical size of about 50 nm (FIGS. **1**C-E).

Administration of ZIKVLPs is Immunogenic and Protects Highly ZIKV Susceptible α/β/γ Interferon Deficient (AG129) Mice

[0115] First, the LD50 of the H/PF/2013 strain in 12 week-old mixed sex AG129 mice was determined. Groups

of mice (n=5) were infected with 5-fold serial dilutions from 2 PFU to 0.02PFU of ZIKV and monitored for 4 weeks following the last mortality. All mice infected with 2 or 0.4 PFU died within the first week of challenge (FIG. **4**), while lower doses killed only 1 to 2 mice within the first two weeks. Interestingly, 2 mice infected with 0.2 PFU ZIKV became ill and were euthanized due to weight loss and paralysis 4.5 weeks following challenge. The resultant LD_{50} value in PFUs was calculated to be 0.19 PFU by the Reed-Muench (REED and MUENCH, 1938) method.

[0116] To determine if ZIKVLPs are immunogenic and protective in highly susceptible AG129 mice, groups of mice received a prime and boost of 450ng ZIKVLPs. AG129 mice that received ZIKVLPs developed low levels (GMT=1:9.2) of neutralizing antibodies (nAbs) at two weeks post administration (FIG. **2**A), that increased two weeks after boost (GMT=1:32). Five weeks after primary vaccination, all mice were challenged with 200 PFU (>1000 LD_{50}s) of ZIKV by the ID route. Mice administered ZIKVLPs maintained weight, while mice that received PBS/alum experienced significant morbidity throughout the challenge period (FIG. **20**B). All control mice (survival 0/6) died 9 days after ZIKV challenge and had significantly lower survival (p=0.0016) than mice administered ZIKVLPs (survival 5/5, FIGS. **2**B and C). Finally. ZIKVLPs vaccinated mice had significantly lower levels of viremia on day 2 post challenge than control mice detected by qRT-PCR (ZIKVLP=1.3×10^4 RNA copies, PBS/alum 9.6×10^7 RNA copies, p=0.0356, FIG. **2**D) and TCID50 assay (ZIKVLP=1.3×10^2 TCID50s, PBS/alum 2.8×10^5 $TCID_{50}$s p=0.0493, FIG. **2**E).

ZIKVLPs Elicit Plaque Reducing Neutralizing Antibody Titers in Mice That Can Be Passively Transferred to Naïve Mice.

[0117] The plaque reduction neutralization test (PRNT) assay is widely considered to be the "gold standard" for characterizing and quantifying circulating levels of anti-dengue and other flaviviral neutralizing antibodies (nAb) (Thomas et al., 2009). A PRNT assay was developed for rapidly measuring ZIKV specific neutralizing antibodies. Pooled serum samples collected from mice pre-challenge, as well as individual serum samples collected from mice post-challenge were tested by this PRNT assay. Pre challenge, pooled serum from mice administered ZIKVLPs had a calculated 50% plaque reduction ($PRNT_{50}$) titer of 1:157. The $PRNT_{50}$ titer increased 2 weeks post challenge (GMT=5122) (FIG. **2**F).

[0118] To test the role of anti-ZIKV antibodies in protection against challenge, groups of mice received ZIKVLP antiserum (pooled pre challenge serum, titer in FIG. **2**F), undiluted (n=5), diluted 1:5 (n=4), or 1:10 (n=4). As a negative control, mice (n=5) were transferred serum from mice previously vaccinated with PBS alum. Negative control mice rapidly lost weight starting after day 7 and all died day 9 post challenge (FIGS. **3**A-B). Mice that received undiluted serum maintained weight throughout the 14 day period post challenge, and showed no signs of infection. Mice that received diluted anti-ZIKV antibodies were not protected from challenge, although survival and weight loss were slightly extended relative to negative control mice (FIGS. **3**A-B).

A Single Dose of ZIKVLPs Can Protect Highly Susceptible AG129 Mice

[0119] To determine if a single dose could protect AG129 mice, groups of 6-week old AG129 mice were vaccinated with 3 μg ZIKVLPs adjuvanted with alum. An additional group of mice (n=5) was vaccinated with a prime and boost of 0.45 μg adjuvanted with alum for comparison. Negative control mice (n=5) received a prime and boost of PBS/alum. Vaccinated mice developed neutralizing antibodies measured by PRNT assay prior to challenge (FIG. **17**A). Eight weeks following primary vaccination mice were challenged with 200 PFU (>1000LD_{50}s) of ZIKV by the ID route. All mice administered a prime of 3 μg or a prime and boost of 0.45 μg ZIKVLPs survived throughout the 6 week challenge period (FIG. **17**C) and maintained weight throughout the challenge period. Pre challenge neutralizing antibody titers in both single (GMT PRNT50=288, PRNT90=81) and double dose (GMT PRNT50=235, PRNT90=50) groups increased significantly ($p<0.005$) in all animals measured at 3 weeks post challenge (FIGS. **17**A-B).

ZIKVLPS Protect Wildtype BALB/c Mice

[0120] To determine if ZIKVLPs can protect wildtype BALB/c mice against non-lethal ZIKV challenge, a group (n=6) was vaccinated with a single dose of 3 ZIKVLPS adjuvanted with alum. Negative control mice (n=5) were administered PBS/alum. Eight weeks after vaccination mice were challenged with 200 PFU ZIKV by the IV route. A single dose of ZIKVLPs elicited high titers of neutralizing antibodies (PRNT50=381, PRNT90=75) detected immediately prior to challenge (FIG. **22**A). Mice vaccinated with ZIKVLPS were completely protected from viremia on day 2 post challenge (FIG. **18**B), and maintained weight throughout the challenge period (FIG. **18**C). Negative control animals lost minor amounts of weight beginning at day 2 post challenge, had high levels of viremia and recovered by 2 weeks post challenge. Neutralizing antibodies were undetectable in negative control mice prior to challenge, but increased significantly after challenge (FIG. **18**A). Antibody titers in vaccinated mice decreased, but were not significantly different than before ZIKV challenge (FIG. **18**A).

DISCUSSION

[0121] Most experts and public health workers agree that a Zika vaccine is urgently needed. In February 2016, the World Health Organization declared that the recent clusters of microcephaly and other neurological disorders in Brazil constitute a public health emergency of international concern. Their recommendations included enhanced surveillance and research, as well as aggressive measures to reduce infection with Zika virus, particularly amongst pregnant women and women of childbearing age. ZIKV is now receiving considerable attention due to its rapid spread in the Americas, and its association with microcephaly (Mlakar et al., 2016) and Guillain-Barre syndrome (Pinto Junior et al., 2015). In these studies, a ZIKV-virus-like particle (VLP) vaccine was designed and it was expressed in vitro as shown by western blot and transmission electron microscopy, and its protective efficacy and role of antibodies in protection in the AG129 mouse model tested. An overall yield of 2.2 mg/L was calculated for the VLP tested. Similar expression levels have been reported for other flavivirus VLP expression strategies (Pijlman, 2015). Future work will optimize VLP

production and purification parameters, which should significantly increase both yield and purity. Stably transfected HEK cells that continuously express VLPs allow for scalable production to help meet global demand for a ZIKV vaccine, which is estimated to be 100 million doses a year.

[0122] ZIKV-VLPs, formulated with alum, induced detectable neutralizing antibodies and protected animals against lethal challenge (>400 LD_{50}s) with no morbidity or mortality. Pre-challenge GMT neutralizing titers were 1:32, and pooled pre-challenge serum $PRNT_{90}$ and $PRNT_{50}$ titers were 1:34 and 1:157 respectively. At a relatively low dose of 450 ng, our results indicate that our ZIKVLPs are highly immunogenic. The antibody titers obtained are consistent with those reported for other highly immunogenic flavivirus VLP vaccines (Ohtaki et al., 2010; Pijlman, 2015). Previous work has shown a direct correlation between dose of VLPs and neutralizing antibody titers. For ZIKV, questions remain about the quantitative relationship between dose of VLPs and their effect on neutralizing antibody titers and protection from ZIKV challenge in vivo.

[0123] In the above-described studies, mice were vaccinated with ZIKVLPS and challenged with a homologous strain of ZIKV (H/PF/2013), which raises the question of ZIKVLP specific antibody cross reactivity to heterologous viruses currently circulating in the Americas. Although the H/PF/2013 virus was isolated well before the current outbreak from a patient infected in French Polynesia, there is a high degree of amino acid similarity (about 99%) to endemic South American strains of ZIKV (Faria et al., 2016; Zanluca et al., 2015). Some experts agree that the high serological cross-reactivity among ZIKV strains would allow for a monovalent vaccine (Lazear and Diamond, 2016). Nevertheless, care must be taken to empirically determine if antibody responses elicited by ZIKV LPs cross-react and protect against South American strains. Finally, any future ZIKV vaccination programs should incorporate careful surveillance of circulating strains to help suppress immunological escape, and ensure efficacy of vaccines in human populations.

[0124] Vaccinated AG129 mice challenged with >1000 LD_{50}s had low levels of viremia (1.3×10^2 $TCID_{50}$s, FIG. **2**E) detected after challenge. Copies of RNA ZIKV genomes in serum of mice were significantly higher than levels of viremia. However, the disparity between viral genome copies and viremia has been observed for other flaviviruses including dengue (Bae et al., 2003). Since AG129 mice are highly susceptible to viral challenge, it is possible that the challenge dose given for the active vaccination study was artificially high. Methods for challenging mice from infected mosquito bite should be developed to most accurately mimic natural infection. The most important criteria for any ZIKV vaccine is its ability to prevent placental and fetal pathology in ZIKV infected pregnant women. Recently developed IFN deficient pregnant mouse models can provide an opportunity to assess if vaccination of pregnant animals can protect the fetus from ZIKV-induced pathology. (Miner et al., 2016). Although models for ZIKV infection in pregnant non-human primates (NHP) are still being developed, ZIKV vaccines should be tested in NHP translational models which most accurately mimics human immune responses to vaccination.

[0125] A VLP vaccine approach against ZIKV has significant advantages over other technologies as it will eliminate concerns of live attenuated vaccines and insufficient inactivation of killed vaccines for pregnant women and other populations at high risk of suffering the devastating effects of ZIKV infections. Production of inactivated vaccines requires high titer growth of infectious virus which may pose a safety concern for workers. Additionally, the production of both attenuated and inactivated ZIKV vaccines is limited to "batch" production, whereas flavirus VLPs can continuously expressed from stable cell lines. In recent years, recombinant virus-like particle (VLP)-based vaccine strategies have been frequently used for vaccine design. VLPs are known to be highly immunogenic and elicit higher titer neutralizing antibody responses than subunit vaccines based on individual proteins (Ariano et al., 2010).

[0126] The role of neutralizing antibodies in protecting against ZIKV was demonstrated by antibody passive transfer studies as naive AG129 mice receiving pooled serum from VLP vaccinated animals were fully protected. These results are consistent with previous findings that indicate the important role of antibodies in protecting against many insect-borne flaviviruses, such as Japanese encephalitis, west Nile virus, and tick borne encephalitis (Chiba et al., 1999; Kimura-Kuroda and Yasui, 1988; Tesh et al., 2002), even at low levels of circulating antibodies. In this study, full protection was observed when animals received undiluted serum ($PRNT_{50}$ 1:157), with no weight loss or other clinical signs observed. While these studies highlight the importance of serum antibodies in ZIKV protection, there are still many important questions related to ZIKV immunology. What is the minimum antibody titer needed for protection, do ZIKVLPs elicit CD8+ responses and are these responses involved in protection, and what is the overall role of cellular immunity in protection? It is also important to determine if anti-ZIKV antibodies, particularly those elicited by ZIKVLPs, play any role in dengue protection or disease enhancement.

[0127] In this study AG129 IFN receptor-deficient mice were used. This mouse models are commonly used for the evaluation of arboviral vaccines, including dengue, chikungunya and yellow fever virus (Meier et al., 2009; Partidos et al., 2011; Prestwood et al., 2012). We recently documented the suitability of mice deficient in IFN-α/β and -γ receptors as an animal model for ZIKV, as they are highly susceptible to ZIKV infection and disease, developing rapid viremic dissemination in visceral organs and brain and dying 7-8 days post-infection (Aliota et al., 2016), and evaluated doses as low as 1 PFU. In our current studies we observed consistent lethality at doses below 1 PFU, indicating that there are viral subpopulations refractory for the formation of CPE in cell culture, but still capable of establishing a lethal infection in highly susceptible mice. It is of great interest is that at a very low dose (0.2PFU) two of five mice became ill more than 1 month after infection, as infection with ZIKV typically produces rapid lethality in AG129 mice.

[0128] The current studies challenged mice with 200 PFU at 11 weeks of age. All control mice lost 20% weight, were moribund, and succumbed to by challenge by day 9. ZIKV challenge therefore appears to be completely lethal in both juvenile and adult AG129 mice. The AG129 mouse model exhibits an intact adaptive immune system, despite the lack of an IFN response, and it has been used extensively to evaluate vaccines and antivirals for DENV (Brewoo et al., 2012; Fuchs et al., 2014; Johnson and Roehrig, 1999; Sarathy et al., 2015). In our studies WT BALB/c mice did not succumb to infection with ZIKV consistent with previous studies where BALB/c mice were experimentally inocu-

lated with 200 PFU of ZIKV (Larocca et al., 2016). Mice also developed high levels of viremia following IV inoculation. A single dose of VLPs prevented detection of viral RNA copies in serum of vaccinated mice at 2 days post infection—when viremia levels typically peak in the BALB/c model. It is possible that viral replication was completely inhibited, as there was no "boost" response in neutralizing antibodies observed following challenge. Finally, in repeat AG129, and Balb/c mice mouse studies, animals were protected from ZIKV challenge 8 weeks after vaccination. ZIKVLP therefore appear to elicit a potent "memory" response.

[0129] In the present study, aluminum hydroxide (commonly known as alum) was used as the adjuvant for ZIKV-VLP preparations. Since its first use in 1932, vaccines containing aluminum-based adjuvants have been successfully administered in humans demonstrating excellent safety. Adjuvant formulations of ZIKV-VLP may facilitate antigen dose sparing, enhanced immunogenicity, and broadened pathogen protection.

[0130] In summary, a vaccine against ZIKV is currently unavailable, nor is there any specific prophylactic treatment. A VLP based Zika vaccine that elicits protective antibodies in mice, and is safe, suitable for scalable production, and highly immunogenic, is disclosed herein. Fast-tracking development of this ZIKV vaccine is a public health priority and is crucial for restoring confidence and security to people who wish to have children or reside in, or visit areas in which ZIKV is endemic.

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gagcaccacc tgagaggaga gtgccagagt tgtgtgtaca acatgatggg aaaaagagaa 8940

aagaaacaag gggaatttgg aaaggccaag ggcagccgcg ccatctggta tatgtggcta 9000

ggggctagat ttctagagtt cgaagccctt ggattcttga acgaggatca ctggatgggg 9060

agagagaact caggaggtgg tgttgaaggg ctgggattac aaagactcgg atatgtccta 9120

gaagagatga gtcgcatacc aggaggaagg atgtatgcag atgacactgc tggctgggac 9180

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acccgcatca gcaggtttga tctggagaat gaagctctaa tcaccaacca aatggagaaa   9240

gggcacaggg ccttggcatt ggccataatc aagtacacat accaaaacaa agtggtaaag   9300

gtccttagac cagctgaaaa agggaagaca gttatggaca ttatttcgag acaagaccaa   9360

agggggagcg gacaagttgt cacttacgct cttaacacat ttaccaacct agtggtgcaa   9420

ctcattcgga gtatggaggc tgaggaagtt ctagagatgc aagacttgtg gctgctgcgg   9480

aggtcagaga aagtgaccaa ctggctgcag agcaacggat gggataggct caaacgaatg   9540

gcagtcagtg gagatgattg cgttgtgagg ccaattgatg ataggtttgc acatgccctc   9600

aggttcttga atgatatggg gaaagttagg aaggacacac aagagtggaa accctcaact   9660

ggatgggaca actgggagga agttccgttt tgctcccacc acttcaacaa gctccatctc   9720

aaggacggga ggtccattgt ggttccctgc cgccaccaag atgaactgat tggccgggcc   9780

cgcgtctctc caggggcggg atggagcatc cgggagactg cttgcctagc aaaatcatat   9840

gcgcaaatgt ggcagctcct ttatttccac agaagggacc tccgactgat ggccaatgcc   9900

atttgttcat ctgtgccagt tgactgggtt ccaactggga gaactacctg gtcaatccat   9960

ggaaagggag aatggatgac cactgaagac atgcttgtgg tgtggaacag agtgtggatt  10020

gaggagaacg accacatgga agacaagacc ccagttacga aatggacaga cattccctat  10080

ttgggaaaaa gggaagactt gtggtgtgga tctctcatag ggcacagacc gcgcaccacc  10140

tgggctgaga acattaaaaa cacagtcaac atggtgcgca ggatcatagg tgatgaagaa  10200

aagtacatgg actacctatc cacccaagtt cgctacttgg gtgaagaagg gtctacacct  10260

ggagtgctgt aa                                                      10272
```

<210> SEQ ID NO 4
<211> LENGTH: 392
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic oligonucleotide

<400> SEQUENCE: 4

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agcctccgcg gccgggaacg gtgcattgga acgcggattc cccgtgccaa gagtgactca    120

ccgtccggat ctcagcaagc aggtatgtac tctccagggt gggcctggct tccccagtca    180

agactccagg gatttgaggg acgctgtggg ctcttctctt acatgtacct tttgcttgcc    240

tcaaccctga ctatcttcca ggtcaggatc ccagagtcag gggtctgtat tttcctgctg    300

gtggctccag ttcaggaaca gtaaaccctg ctccgaatat tgcctctcac atctcgtcaa    360

tctccgcgag gactggggac cctgtgacga ac                                  392
```

<210> SEQ ID NO 5
<211> LENGTH: 4251
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(4251)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 5

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tgttgatact catactcttc ctttttcata ttattgaagc atttatcagg gttattgtct 60

catgagccnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn anaantnngg gttccccgcn 120

cattnccccg aaaagtgcca cctgacgtcg ncggatcggg agatctccnn nnnnnnnnnn 180

nnnnnnnnnn nnnnnnnnnn gctctgatgc cgcatagtta agccagtatc tgctccctgc 240

ttgtgtgttg gaggtcgctg agtagtgcnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 300

cttgaccgac aattgcatga agaatctgct tagggttagg cgttttgcgc tgcttcgcga 360

tgtacggcnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn agttattaat agtaatcaat 420

tacggggtca ttagttcata gcccatatat ggagttccgc gttacatann nnnnnnnnnn 480

nnnnnnnnnn nnnnnnnnnn cgaacgaccc ccgcccattg acgtcaataa tgacgtatgt 540

tcccatagta acgccaatag ggactttcnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 600

aactgcccac ttggcagtac atcaagtgta tcatatgcca agtccgcccc ctattgacgt 660

caatgaccnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn aactgcccac ttggcagtac 720

atcaagtgta tcatatgcca agtccgcccc ctattgacgt caatgaccnn nnnnnnnnnn 780

nnnnnnnnnn nnnnnnnnnn agcggtttga ctcacgggga tttccaagtc tccaccccat 840

tgacgtcaat gggagtttgt tttggcacnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 900

taaccccgcc ccgttgacgc aaatgggcgg taggcgtgta cggtgggagg tctatataag 960

cagagctcnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn catccacgct gttttgacct 1020

ccatagaaga caccgggacc gatccagcct ccgcggccgg gaacggtcnn nnnnnnnnnn 1080

nnnnnnnnnn nnnnnnnnnn actcaccgtc cggatctcag caagcaggta tgtactctcc 1140

agggtgggcc tggcttcccc agtcaagann nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 1200

ctcttacatg taccttttgc ttgcctcaac cctgactatc ttccaggtca ggatcccaga 1260

gtcagggcnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn gaacagtaaa ccctgctccg 1320

aatattgcct ctcacatctc gtcaatctcc gcgaggactg gggaccctnn nnnnnnnnnn 1380

nnnnnnnnnn nnnnnnnnnn cctcctgctg accacagcta tggcagcgga ggtcactaga 1440

cgtgggagtg catactatat gtacttgcnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 1500

ccaaccacat tggggatgaa taagtgttat atacagatca tggatcttgg acacatgtgt 1560

gatgccacnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn gggtggaacc agatgacgtc 1620

gattgttggt gcaacacgac gtcaacttgg gttgtgtacg gaacctgcnn nnnnnnnnnn 1680

nnnnnnnnnn nnnnnnnnnn aagagctgtg acgctcccct cccattccac tagtttgctg 1740

caaacgcggt cgcaaacctg gttggaatnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 1800

gaaaattgga tattcaggaa ccctggcttc gcgttagcag cagctgccat cgcttggctt 1860

ttgggaatnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn tgatactgct gattgccccg 1920

gcatacagca tcaggtgcat aggagtcagc aatagggact ttgtggaann nnnnnnnnnn 1980

nnnnnnnnnn nnnnnnnnnn cttggaacat ggaggttgtg tcaccgtaat ggcacaggac 2040

aaaccgactg tcgacataga gctggttann nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 2100

tcctactgct atgaggcatc aatatcggac atggcttcgg acagccgctg cccaacacaa 2160

ggtgaagcnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn tctgcaaaag aacgttagtg 2220

gacagaggct ggggaaatgg atgtggactt tttggcaaag ggagcctcnn nnnnnnnnnn 2280

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nnnnnnnnnn nnnnnnnnnn aatgaccggg aagagcatcc agccagagaa tctggagtac 2340

cggataatgc tgtcagttca tggctcccnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 2400

catgaaactg atgagaatag agcgaaggtt gagataacgc ccaattcacc aagagccgaa 2460

gccaccctnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn aaccgaggac aggccttgac 2520

ttttcagatt tgtattactt gactatgaat aacaagcact ggttggttnn nnnnnnnnnn 2580

nnnnnnnnnn nnnnnnnnnn ttggcacgct ggggcagaca ccggaactcc acactggaac 2640

aacaaagaag cactggtaga gttcaagcnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 2700

ctagggagtc aagaaggagc agttcacacg gcccttgctg gagctctgga ggctgagatg 2760

gatggtgcnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn gtcgcctgaa aatggataaa 2820

cttagattga agggcgtgtc atactccttg tgtaccgcag cgttcacann nnnnnnnnnn 2880

nnnnnnnnnn nnnnnnnnnn gacagtcaca gtggaggtac agtacgcagg gacagatgga 2940

ccttgcaagg ttccagctca gatggcgcnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 3000

ttgataaccg ctaaccccgt aatcactgaa agcactgaga actctaagat gatgctggaa 3060

cttgatccnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn tcggggagaa gaagatcacc 3120

caccactggc acaggagtgg cagcaccatt ggaaaagcat ttgaagccnn nnnnnnnnnn 3180

nnnnnnnnnn nnnnnnnnnn gggagacaca gcctgggact ttggatcagt tggaggcgct 3240

ctcaactcat tgggcaaggg catccatcnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 3300

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aacacaaann nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn taggggggagt gttgatcttc 3420

ttatccacag ctgtctctgc tgatgtgggg tgctcggtgt gaggatctnn nnnnnnnnnn 3480

nnnnnnnnnn nnnnnnnnnn ccctaaactt catgggttac gtaattggaa gttgggggac 3540

attgccacaa gatcatattg tacaaaacnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 3600

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ggctttcact ttctcgccaa cttacaaggc ctttctaagt aaacagtann nnnnnnnnnn 3780

nnnnnnnnnn nnnnnnnnnn ctggtctgtg ccaagtgttt gctgacgcaa cccccactgg 3840

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tctttttccc tctgccaaaa attatgggga catcatgaag ccccttgann nnnnnnnnnn 4080

nnnnnnnnnn nnnnnnnnnn ttttcattgc aatagtgtgt tggaattttt tgtgtctctc 4140

actcggaagg aattctgcat taatgaatnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 4200

ttgggcgctc ttccgcttcc tcgctcactg anctcgntgc gcttcggtcg t 4251

<210> SEQ ID NO 6
<211> LENGTH: 867
<212> TYPE: PRT
<213> ORGANISM: Zika virus

<400> SEQUENCE: 6

Ile Arg Cys Ile Gly Val Ser Asn Arg Asp Phe Val Glu Gly Met Ser
1 5 10 15

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Gly Gly Thr Trp Val Asp Val Val Leu Glu His Gly Gly Cys Val Thr
            20                  25                  30

Val Met Ala Gln Asp Lys Pro Thr Val Asp Ile Glu Leu Val Thr Thr
        35                  40                  45

Thr Val Ser Asn Met Ala Glu Val Arg Ser Tyr Cys Tyr Glu Ala Ser
    50                  55                  60

Ile Ser Asp Met Ala Ser Asp Ser Arg Cys Pro Thr Gln Gly Glu Ala
65                  70                  75                  80

Tyr Leu Asp Lys Gln Ser Asp Thr Gln Tyr Val Cys Lys Arg Thr Leu
                85                  90                  95

Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly Lys Gly Ser
            100                 105                 110

Leu Val Thr Cys Ala Lys Phe Ala Cys Ser Lys Lys Met Thr Gly Lys
        115                 120                 125

Ser Ile Gln Pro Glu Asn Leu Glu Tyr Arg Ile Met Leu Ser Val His
    130                 135                 140

Gly Ser Gln His Ser Gly Met Ile Val Asn Asp Thr Gly His Glu Thr
145                 150                 155                 160

Asp Glu Asn Arg Ala Lys Val Glu Ile Thr Pro Asn Ser Pro Arg Ala
                165                 170                 175

Glu Ala Thr Leu Gly Gly Phe Gly Ser Leu Gly Leu Asp Cys Glu Pro
            180                 185                 190

Arg Thr Gly Leu Asp Phe Ser Asp Leu Tyr Tyr Leu Thr Met Asn Asn
        195                 200                 205

Lys His Trp Leu Val His Lys Glu Trp Phe His Asp Ile Pro Leu Pro
    210                 215                 220

Trp His Ala Gly Ala Asp Thr Gly Thr Pro His Trp Asn Asn Lys Glu
225                 230                 235                 240

Ala Leu Val Glu Phe Lys Asp Ala His Ala Lys Arg Gln Thr Val Val
                245                 250                 255

Val Leu Gly Ser Gln Glu Gly Ala Val His Thr Ala Leu Ala Gly Ala
            260                 265                 270

Leu Glu Ala Glu Met Asp Gly Ala Lys Gly Arg Leu Ser Ser Gly His
        275                 280                 285

Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Arg Leu Lys Gly Val Ser
    290                 295                 300

Tyr Ser Leu Cys Thr Ala Ala Phe Thr Phe Thr Lys Ile Pro Ala Glu
305                 310                 315                 320

Thr Leu His Gly Thr Val Thr Val Glu Val Gln Tyr Ala Gly Thr Asp
                325                 330                 335

Gly Pro Cys Lys Val Pro Ala Gln Met Ala Val Asp Met Gln Thr Leu
            340                 345                 350

Thr Pro Val Gly Arg Leu Ile Thr Ala Asn Pro Val Ile Thr Glu Ser
        355                 360                 365

Thr Glu Asn Ser Lys Met Met Leu Glu Leu Asp Pro Pro Phe Gly Asp
    370                 375                 380

Ser Tyr Ile Val Ile Gly Val Gly Glu Lys Lys Ile Thr His His Trp
385                 390                 395                 400

His Arg Ser Gly Ser Thr Ile Gly Lys Ala Phe Glu Ala Thr Val Arg
                405                 410                 415
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Gly Ala Lys Arg Met Ala Val Leu Gly Asp Thr Ala Trp Asp Phe Gly
            420                 425                 430

Ser Val Gly Gly Ala Leu Asn Ser Leu Gly Lys Gly Ile His Gln Ile
        435                 440                 445

Phe Gly Ala Ala Phe Lys Ser Leu Phe Gly Gly Met Ser Trp Phe Ser
    450                 455                 460

Gln Ile Leu Ile Gly Thr Leu Leu Met Trp Leu Gly Leu Asn Thr Lys
465                 470                 475                 480

Asn Gly Ser Ile Ser Leu Met Cys Leu Ala Leu Gly Gly Val Leu Ile
                485                 490                 495

Phe Leu Ser Thr Ala Val Ser Ala Asp Val Gly Cys Ser Val Asp Phe
            500                 505                 510

Ser Lys Lys Glu Thr Arg Cys Gly Thr Gly Val Phe Val Tyr Asn Asp
        515                 520                 525

Val Glu Ala Trp Arg Asp Arg Tyr Lys Tyr His Pro Asp Ser Pro Arg
    530                 535                 540

Arg Leu Ala Ala Ala Val Lys Gln Ala Trp Glu Asp Gly Ile Cys Gly
545                 550                 555                 560

Ile Ser Ser Val Ser Arg Met Glu Asn Ile Met Trp Arg Ser Val Glu
                565                 570                 575

Gly Glu Leu Asn Ala Ile Leu Glu Glu Asn Gly Val Gln Leu Thr Val
            580                 585                 590

Val Val Gly Ser Val Lys Asn Pro Met Trp Arg Gly Pro Gln Arg Leu
        595                 600                 605

Pro Val Pro Val Asn Glu Leu Pro His Gly Trp Lys Ala Trp Gly Lys
    610                 615                 620

Ser Tyr Phe Val Arg Ala Ala Lys Thr Asn Asn Ser Phe Val Val Asp
625                 630                 635                 640

Gly Asp Thr Leu Lys Glu Cys Pro Leu Lys His Arg Ala Trp Asn Ser
                645                 650                 655

Phe Leu Val Glu Asp His Gly Phe Gly Val Phe His Thr Ser Val Trp
            660                 665                 670

Leu Lys Val Arg Glu Asp Tyr Ser Leu Glu Cys Asp Pro Ala Val Ile
        675                 680                 685

Gly Thr Ala Val Lys Gly Lys Glu Ala Val His Ser Asp Leu Gly Tyr
    690                 695                 700

Trp Ile Glu Ser Glu Lys Asn Asp Thr Trp Arg Leu Lys Arg Ala His
705                 710                 715                 720

Leu Ile Glu Met Lys Thr Cys Glu Trp Pro Lys Ser His Thr Leu Trp
                725                 730                 735

Thr Asp Gly Ile Glu Glu Ser Asp Leu Ile Ile Pro Lys Ser Leu Ala
            740                 745                 750

Gly Pro Leu Ser His His Asn Thr Arg Glu Gly Tyr Arg Thr Gln Met
        755                 760                 765

Lys Gly Pro Trp His Ser Glu Glu Leu Glu Ile Arg Phe Glu Glu Cys
    770                 775                 780

Pro Gly Thr Lys Val His Val Glu Glu Thr Cys Gly Thr Arg Gly Pro
785                 790                 795                 800

Ser Leu Arg Ser Thr Thr Ala Ser Gly Arg Val Ile Glu Glu Trp Cys
                805                 810                 815

Cys Arg Glu Cys Thr Met Pro Pro Leu Ser Phe Trp Ala Lys Asp Gly
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            820                 825                 830

Cys Trp Tyr Gly Met Glu Ile Arg Pro Arg Lys Glu Pro Glu Ser Asn
        835                 840                 845

Leu Val Arg Ser Met Val Thr Ala Gly Ser Thr Asp His Met Asp His
    850                 855                 860

Phe Ser Leu
865


<210> SEQ ID NO 7
<211> LENGTH: 3423
<212> TYPE: PRT
<213> ORGANISM: Zika virus

<400> SEQUENCE: 7

Met Lys Asn Pro Lys Lys Lys Ser Gly Gly Phe Arg Ile Val Asn Met
 1               5                  10                  15

Leu Lys Arg Gly Val Ala Arg Val Ser Pro Phe Gly Gly Leu Lys Arg
            20                  25                  30

Leu Pro Ala Gly Leu Leu Leu Gly His Gly Pro Ile Arg Met Val Leu
        35                  40                  45

Ala Ile Leu Ala Phe Leu Arg Phe Thr Ala Ile Lys Pro Ser Leu Gly
    50                  55                  60

Leu Ile Asn Arg Trp Gly Ser Val Gly Lys Lys Glu Ala Met Glu Ile
65                  70                  75                  80

Ile Lys Lys Phe Lys Lys Asp Leu Ala Ala Met Leu Arg Ile Ile Asn
                85                  90                  95

Ala Arg Lys Glu Lys Lys Arg Arg Gly Thr Asp Thr Ser Val Gly Ile
            100                 105                 110

Val Gly Leu Leu Leu Thr Thr Ala Met Ala Val Glu Val Thr Arg Arg
        115                 120                 125

Gly Asn Ala Tyr Tyr Met Tyr Leu Asp Arg Ser Asp Ala Gly Glu Ala
    130                 135                 140

Ile Ser Phe Pro Thr Thr Met Gly Met Asn Lys Cys Tyr Ile Gln Ile
145                 150                 155                 160

Met Asp Leu Gly His Met Cys Asp Ala Thr Met Ser Tyr Glu Cys Pro
                165                 170                 175

Met Leu Asp Glu Gly Val Glu Pro Asp Asp Val Asp Cys Trp Cys Asn
            180                 185                 190

Thr Thr Ser Thr Trp Val Val Tyr Gly Thr Cys His His Lys Lys Gly
        195                 200                 205

Glu Ala Arg Arg Ser Arg Arg Ala Val Thr Leu Pro Ser His Ser Thr
    210                 215                 220

Arg Lys Leu Gln Thr Arg Ser Gln Thr Trp Leu Glu Ser Arg Glu Tyr
225                 230                 235                 240

Thr Lys His Leu Ile Arg Val Glu Asn Trp Ile Phe Arg Asn Pro Gly
                245                 250                 255

Phe Ala Leu Ala Ala Ala Ala Ile Ala Trp Leu Leu Gly Ser Ser Thr
            260                 265                 270

Ser Gln Lys Val Ile Tyr Leu Val Met Ile Leu Leu Ile Ala Pro Ala
        275                 280                 285

Tyr Ser Ile Arg Cys Ile Gly Val Ser Asn Arg Asp Phe Val Glu Gly
    290                 295                 300
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Met Ser Gly Gly Thr Trp Val Asp Val Val Leu Glu His Gly Gly Cys
305                 310                 315                 320

Val Thr Val Met Ala Gln Asp Lys Pro Thr Val Asp Ile Glu Leu Val
                325                 330                 335

Thr Thr Thr Val Ser Asn Met Ala Glu Val Arg Ser Tyr Cys Tyr Glu
            340                 345                 350

Ala Ser Ile Ser Asp Met Ala Ser Asp Ser Arg Cys Pro Thr Gln Gly
        355                 360                 365

Glu Ala Tyr Leu Asp Lys Gln Ser Asp Thr Gln Tyr Val Cys Lys Arg
    370                 375                 380

Thr Leu Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly Lys
385                 390                 395                 400

Gly Ser Leu Val Thr Cys Ala Lys Phe Ala Cys Ser Lys Lys Met Thr
                405                 410                 415

Gly Lys Ser Ile Gln Pro Glu Asn Leu Glu Tyr Arg Ile Met Leu Ser
            420                 425                 430

Val His Gly Ser Gln His Ser Gly Met Ile Val Asn Asp Thr Gly His
        435                 440                 445

Glu Thr Asp Glu Asn Arg Ala Lys Val Glu Ile Thr Pro Asn Ser Pro
    450                 455                 460

Arg Ala Glu Ala Thr Leu Gly Gly Phe Gly Ser Leu Gly Leu Asp Cys
465                 470                 475                 480

Glu Pro Arg Thr Gly Leu Asp Phe Ser Asp Leu Tyr Tyr Leu Thr Met
                485                 490                 495

Asn Asn Lys His Trp Leu Val His Lys Glu Trp Phe His Asp Ile Pro
            500                 505                 510

Leu Pro Trp His Ala Gly Ala Asp Thr Gly Thr Pro His Trp Asn Asn
        515                 520                 525

Lys Glu Ala Leu Val Glu Phe Lys Asp Ala His Ala Lys Arg Gln Thr
    530                 535                 540

Val Val Val Leu Gly Ser Gln Glu Gly Ala Val His Thr Ala Leu Ala
545                 550                 555                 560

Gly Ala Leu Glu Ala Glu Met Asp Gly Ala Lys Gly Arg Leu Ser Ser
                565                 570                 575

Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Arg Leu Lys Gly
            580                 585                 590

Val Ser Tyr Ser Leu Cys Thr Ala Ala Phe Thr Phe Thr Lys Ile Pro
        595                 600                 605

Ala Glu Thr Leu His Gly Thr Val Thr Val Glu Val Gln Tyr Ala Gly
    610                 615                 620

Thr Asp Gly Pro Cys Lys Val Pro Ala Gln Met Ala Val Asp Met Gln
625                 630                 635                 640

Thr Leu Thr Pro Val Gly Arg Leu Ile Thr Ala Asn Pro Val Ile Thr
                645                 650                 655

Glu Ser Thr Glu Asn Ser Lys Met Met Leu Glu Leu Asp Pro Pro Phe
            660                 665                 670

Gly Asp Ser Tyr Ile Val Ile Gly Val Gly Glu Lys Lys Ile Thr His
        675                 680                 685

His Trp His Arg Ser Gly Ser Thr Ile Gly Lys Ala Phe Glu Ala Thr
    690                 695                 700

Val Arg Gly Ala Lys Arg Met Ala Val Leu Gly Asp Thr Ala Trp Asp
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```
705                 710                 715                 720

Phe Gly Ser Val Gly Gly Ala Leu Asn Ser Leu Gly Lys Gly Ile His
                725                 730                 735

Gln Ile Phe Gly Ala Ala Phe Lys Ser Leu Phe Gly Gly Met Ser Trp
            740                 745                 750

Phe Ser Gln Ile Leu Ile Gly Thr Leu Leu Val Trp Leu Gly Leu Asn
        755                 760                 765

Thr Lys Asn Gly Ser Ile Ser Leu Met Cys Leu Ala Leu Gly Gly Val
    770                 775                 780

Leu Ile Phe Leu Ser Thr Ala Val Ser Ala Asp Val Gly Cys Ser Val
785                 790                 795                 800

Asp Phe Ser Lys Lys Glu Thr Arg Cys Gly Thr Gly Val Phe Val Tyr
                805                 810                 815

Asn Asp Val Glu Ala Trp Arg Asp Arg Tyr Lys Tyr His Pro Asp Ser
            820                 825                 830

Pro Arg Arg Leu Ala Ala Ala Val Lys Gln Ala Trp Glu Asp Gly Ile
        835                 840                 845

Cys Gly Ile Ser Ser Val Ser Arg Met Glu Asn Ile Met Trp Arg Ser
    850                 855                 860

Val Glu Gly Glu Leu Asn Ala Ile Leu Glu Glu Asn Gly Val Gln Leu
865                 870                 875                 880

Thr Val Val Val Gly Ser Val Lys Asn Pro Met Trp Arg Gly Pro Gln
                885                 890                 895

Arg Leu Pro Val Pro Val Asn Glu Leu Pro His Gly Trp Lys Ala Trp
            900                 905                 910

Gly Lys Ser Tyr Phe Val Arg Ala Ala Lys Thr Asn Asn Ser Phe Val
        915                 920                 925

Val Asp Gly Asp Thr Leu Lys Glu Cys Pro Leu Lys His Arg Ala Trp
    930                 935                 940

Asn Ser Phe Leu Val Glu Asp His Gly Phe Gly Val Phe His Thr Ser
945                 950                 955                 960

Val Trp Leu Lys Val Arg Glu Asp Tyr Ser Leu Glu Cys Asp Pro Ala
                965                 970                 975

Val Ile Gly Thr Ala Ala Lys Gly Lys Glu Ala Val His Ser Asp Leu
            980                 985                 990

Gly Tyr Trp Ile Glu Ser Glu Lys Asn Asp Thr Trp Arg Leu Lys Arg
        995                 1000                1005

Ala His Leu Ile Glu Met Lys Thr Cys Glu Trp Pro Lys Ser His Thr
   1010                1015                1020

Leu Trp Thr Asp Gly Ile Glu Glu Ser Asp Leu Ile Ile Pro Lys Ser
1025                1030                1035                1040

Leu Ala Gly Pro Leu Ser His His Asn Thr Arg Glu Gly Tyr Arg Thr
               1045                1050                1055

Gln Met Lys Gly Pro Trp His Ser Glu Glu Leu Glu Ile Arg Phe Glu
          1060                1065                1070

Glu Cys Pro Gly Thr Lys Val His Val Glu Glu Thr Cys Gly Thr Arg
       1075                1080                1085

Gly Pro Ser Leu Arg Ser Thr Thr Ala Ser Gly Arg Val Ile Glu Glu
   1090                1095                1100

Trp Cys Cys Arg Glu Cys Thr Met Pro Pro Leu Ser Phe Arg Ala Lys
1105                1110                1115                1120
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Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Arg Lys Glu Pro Glu
             1125                1130                1135

Ser Asn Leu Val Arg Ser Met Val Thr Ala Gly Ser Thr Asp His Met
          1140                1145                1150

Asp His Phe Ser Leu Gly Val Leu Val Ile Leu Leu Met Val Gln Glu
       1155                1160                1165

Gly Leu Lys Lys Arg Met Thr Thr Lys Ile Ile Ile Ser Thr Ser Met
   1170                1175                1180

Ala Val Leu Val Ala Met Ile Leu Gly Gly Phe Ser Met Ser Asp Leu
1185                1190                1195                1200

Ala Lys Leu Ala Ile Leu Met Gly Ala Thr Phe Ala Glu Met Asn Thr
             1205                1210                1215

Gly Gly Asp Val Ala His Leu Ala Leu Ile Ala Ala Phe Lys Val Arg
          1220                1225                1230

Pro Ala Leu Leu Val Ser Phe Ile Phe Arg Ala Asn Trp Thr Pro Arg
       1235                1240                1245

Glu Ser Met Leu Leu Ala Leu Ala Ser Cys Leu Leu Gln Thr Ala Ile
   1250                1255                1260

Ser Ala Leu Glu Gly Asp Leu Met Val Pro Ile Asn Gly Phe Ala Leu
1265                1270                1275                1280

Ala Trp Leu Ala Ile Arg Ala Met Val Val Pro Arg Thr Asp Asn Ile
             1285                1290                1295

Thr Leu Ala Ile Leu Ala Ala Leu Thr Pro Leu Ala Arg Gly Thr Leu
          1300                1305                1310

Leu Val Ala Trp Arg Ala Gly Leu Ala Thr Cys Gly Gly Phe Met Leu
       1315                1320                1325

Leu Ser Leu Lys Gly Lys Gly Ser Val Lys Lys Asn Leu Pro Phe Val
   1330                1335                1340

Met Ala Leu Gly Leu Thr Ala Val Arg Leu Val Asp Pro Ile Asn Val
1345                1350                1355                1360

Val Gly Leu Leu Leu Leu Thr Arg Ser Gly Lys Arg Ser Trp Pro Pro
             1365                1370                1375

Ser Glu Val Leu Thr Ala Val Gly Leu Ile Cys Ala Leu Ala Gly Gly
          1380                1385                1390

Phe Ala Lys Ala Asp Ile Glu Met Ala Gly Pro Met Ala Ala Val Gly
       1395                1400                1405

Leu Leu Ile Val Ser Tyr Val Val Ser Gly Lys Ser Val Asp Met Tyr
   1410                1415                1420

Ile Glu Arg Ala Gly Asp Ile Thr Trp Glu Lys Asp Ala Glu Val Thr
1425                1430                1435                1440

Gly Asn Ser Pro Arg Leu Asp Val Ala Leu Asp Glu Ser Gly Asp Phe
             1445                1450                1455

Ser Leu Val Glu Asp Asp Gly Pro Pro Met Arg Glu Ile Ile Leu Lys
          1460                1465                1470

Val Val Leu Met Ala Ile Cys Gly Met Asn Pro Ile Ala Ile Pro Phe
       1475                1480                1485

Ala Ala Gly Ala Trp Tyr Val Tyr Val Lys Thr Gly Lys Arg Ser Gly
   1490                1495                1500

Ala Leu Trp Asp Val Pro Ala Pro Lys Glu Val Lys Lys Gly Glu Thr
1505                1510                1515                1520
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Thr Asp Gly Val Tyr Arg Val Met Thr Arg Arg Leu Leu Gly Ser Thr
              1525                1530                1535

Gln Val Gly Val Gly Val Met Gln Glu Gly Val Phe His Thr Met Trp
          1540                1545                1550

His Val Thr Lys Gly Ser Ala Leu Arg Ser Gly Glu Gly Arg Leu Asp
      1555                1560                1565

Pro Tyr Trp Gly Asp Val Lys Gln Asp Leu Val Ser Tyr Cys Gly Pro
  1570                1575                1580

Trp Lys Leu Asp Ala Ala Trp Asp Gly His Ser Glu Val Gln Leu Leu
1585                1590                1595                1600

Ala Val Pro Pro Gly Glu Arg Ala Arg Asn Ile Gln Thr Leu Pro Gly
              1605                1610                1615

Ile Phe Lys Thr Lys Asp Gly Asp Ile Gly Ala Val Ala Leu Asp Tyr
          1620                1625                1630

Pro Ala Gly Thr Ser Gly Ser Pro Ile Leu Asp Lys Cys Gly Arg Val
      1635                1640                1645

Ile Gly Leu Tyr Gly Asn Gly Val Val Ile Lys Asn Gly Ser Tyr Val
  1650                1655                1660

Ser Ala Ile Thr Gln Gly Arg Arg Glu Glu Glu Thr Pro Val Glu Cys
1665                1670                1675                1680

Phe Glu Pro Ser Met Leu Lys Lys Lys Gln Leu Thr Val Leu Asp Leu
              1685                1690                1695

His Pro Gly Ala Gly Lys Thr Arg Arg Val Leu Pro Glu Ile Val Arg
          1700                1705                1710

Glu Ala Ile Lys Thr Arg Leu Arg Thr Val Ile Leu Ala Pro Thr Arg
      1715                1720                1725

Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu Pro Val Arg
  1730                1735                1740

Tyr Met Thr Thr Ala Val Asn Val Thr His Ser Gly Thr Glu Ile Val
1745                1750                1755                1760

Asp Leu Met Cys His Ala Thr Phe Thr Ser Arg Leu Leu Gln Pro Ile
              1765                1770                1775

Arg Val Pro Asn Tyr Asn Leu Tyr Ile Met Asp Glu Ala His Phe Thr
          1780                1785                1790

Asp Pro Ser Ser Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Glu
      1795                1800                1805

Met Gly Glu Ala Ala Ala Ile Phe Met Thr Ala Thr Pro Pro Gly Thr
  1810                1815                1820

Arg Asp Ala Phe Pro Asp Ser Asn Ser Pro Ile Met Asp Thr Glu Val
1825                1830                1835                1840

Glu Val Pro Glu Arg Ala Trp Ser Ser Gly Phe Asp Trp Val Thr Asp
              1845                1850                1855

His Ser Gly Lys Thr Val Trp Phe Val Pro Ser Val Arg Asn Gly Asn
          1860                1865                1870

Glu Ile Ala Ala Cys Leu Thr Lys Ala Gly Lys Arg Val Ile Gln Leu
      1875                1880                1885

Ser Arg Lys Thr Phe Glu Thr Glu Phe Gln Lys Thr Lys His Gln Glu
  1890                1895                1900

Trp Asp Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe
1905                1910                1915                1920

Lys Ala Asp Arg Val Ile Asp Ser Arg Arg Cys Leu Lys Pro Val Ile
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             1925                1930                1935

Leu Asp Gly Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr His
          1940                1945                1950

Ala Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro Asn Lys
       1955                1960                1965

Pro Gly Asp Glu Tyr Leu Tyr Gly Gly Gly Cys Ala Glu Thr Asp Glu
   1970                1975                1980

Asp His Ala His Trp Leu Glu Ala Arg Met Leu Leu Asp Asn Ile Tyr
1985                1990                1995                2000

Leu Gln Asp Gly Leu Ile Ala Ser Leu Tyr Arg Pro Glu Ala Asp Lys
             2005                2010                2015

Val Ala Ala Ile Glu Gly Glu Phe Lys Leu Arg Thr Glu Gln Arg Lys
          2020                2025                2030

Thr Phe Val Glu Leu Met Lys Arg Gly Asp Leu Pro Val Trp Leu Ala
       2035                2040                2045

Tyr Gln Val Ala Ser Ala Gly Ile Thr Tyr Thr Asp Arg Arg Trp Cys
   2050                2055                2060

Phe Asp Gly Thr Thr Asn Asn Thr Ile Met Glu Asp Ser Val Pro Ala
2065                2070                2075                2080

Glu Val Trp Thr Arg Tyr Gly Glu Lys Arg Val Leu Lys Pro Arg Trp
             2085                2090                2095

Met Asp Ala Arg Val Cys Ser Asp His Ala Ala Leu Lys Ser Phe Lys
          2100                2105                2110

Glu Phe Ala Ala Gly Lys Arg Gly Ala Ala Phe Gly Val Met Glu Ala
       2115                2120                2125

Leu Gly Thr Leu Pro Gly His Met Thr Glu Arg Phe Gln Glu Ala Ile
   2130                2135                2140

Asp Asn Leu Ala Val Leu Met Arg Ala Glu Thr Gly Ser Arg Pro Tyr
2145                2150                2155                2160

Lys Ala Ala Ala Ala Gln Leu Pro Glu Thr Leu Glu Thr Ile Met Leu
             2165                2170                2175

Leu Gly Leu Leu Gly Thr Val Ser Leu Gly Ile Phe Phe Val Leu Met
          2180                2185                2190

Arg Asn Lys Gly Ile Gly Lys Met Gly Phe Gly Met Val Thr Leu Gly
       2195                2200                2205

Ala Ser Ala Trp Leu Met Trp Leu Ser Glu Ile Glu Pro Ala Arg Ile
   2210                2215                2220

Ala Cys Val Leu Ile Val Val Phe Leu Leu Leu Val Val Leu Ile Pro
2225                2230                2235                2240

Glu Pro Glu Lys Gln Arg Ser Pro Gln Asp Asn Gln Met Ala Ile Ile
             2245                2250                2255

Ile Met Val Ala Val Gly Leu Leu Gly Leu Ile Thr Ala Asn Glu Leu
          2260                2265                2270

Gly Trp Leu Glu Arg Thr Lys Ser Asp Leu Ser His Leu Met Gly Arg
       2275                2280                2285

Arg Glu Glu Gly Ala Thr Ile Gly Phe Ser Met Asp Ile Asp Leu Arg
   2290                2295                2300

Pro Ala Ser Ala Trp Ala Ile Tyr Ala Ala Leu Thr Thr Phe Ile Thr
2305                2310                2315                2320

Pro Ala Val Gln His Ala Val Thr Thr Ser Tyr Asn Asn Tyr Ser Leu
             2325                2330                2335
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Met Ala Met Ala Thr Gln Ala Gly Val Leu Phe Gly Met Gly Lys Gly
          2340                2345                2350

Met Pro Phe Tyr Ala Trp Asp Phe Gly Val Pro Leu Leu Met Ile Gly
       2355                2360                2365

Cys Tyr Ser Gln Leu Thr Pro Leu Thr Leu Ile Val Ala Ile Ile Leu
   2370                2375                2380

Leu Val Ala His Tyr Met Tyr Leu Ile Pro Gly Leu Gln Ala Ala Ala
2385                2390                2395                2400

Ala Arg Ala Ala Gln Lys Arg Thr Ala Ala Gly Ile Met Lys Asn Pro
               2405                2410                2415

Val Val Asp Gly Ile Val Val Thr Asp Ile Asp Thr Met Thr Ile Asp
          2420                2425                2430

Pro Gln Val Glu Lys Lys Met Gly Gln Val Leu Leu Ile Ala Val Ala
       2435                2440                2445

Val Ser Ser Ala Ile Leu Ser Arg Thr Ala Trp Gly Trp Gly Glu Ala
   2450                2455                2460

Gly Ala Leu Ile Thr Ala Ala Thr Ser Thr Leu Trp Glu Gly Ser Pro
2465                2470                2475                2480

Asn Lys Tyr Trp Asn Ser Ser Thr Ala Thr Ser Leu Cys Asn Ile Phe
               2485                2490                2495

Arg Gly Ser Tyr Leu Ala Gly Ala Ser Leu Ile Tyr Thr Val Thr Arg
          2500                2505                2510

Asn Ala Gly Leu Val Lys Arg Arg Gly Gly Gly Thr Gly Glu Thr Leu
       2515                2520                2525

Gly Glu Lys Trp Lys Ala Arg Leu Asn Gln Met Ser Ala Leu Glu Phe
   2530                2535                2540

Tyr Ser Tyr Lys Lys Ser Gly Ile Thr Glu Val Cys Arg Glu Glu Ala
2545                2550                2555                2560

Arg Arg Ala Leu Lys Asp Gly Val Ala Thr Gly Gly His Ala Val Ser
               2565                2570                2575

Arg Gly Ser Ala Lys Leu Arg Trp Leu Val Glu Arg Gly Tyr Leu Gln
          2580                2585                2590

Pro Tyr Gly Lys Val Ile Asp Leu Gly Cys Gly Arg Gly Gly Trp Ser
       2595                2600                2605

Tyr Tyr Ala Ala Thr Ile Arg Lys Val Gln Glu Val Lys Gly Tyr Thr
   2610                2615                2620

Lys Gly Gly Pro Gly His Glu Glu Pro Met Leu Val Gln Ser Tyr Gly
2625                2630                2635                2640

Trp Asn Ile Val Arg Leu Lys Ser Gly Val Asp Val Phe His Met Ala
               2645                2650                2655

Ala Glu Pro Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Ser
          2660                2665                2670

Ser Pro Glu Val Glu Glu Ala Arg Thr Leu Arg Val Leu Ser Met Val
       2675                2680                2685

Gly Asp Trp Leu Glu Lys Arg Pro Gly Ala Phe Cys Ile Lys Val Leu
   2690                2695                2700

Cys Pro Tyr Thr Ser Thr Met Met Glu Thr Leu Glu Arg Leu Gln Arg
2705                2710                2715                2720

Arg Tyr Gly Gly Gly Leu Val Arg Val Pro Leu Ser Arg Asn Ser Thr
               2725                2730                2735
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His Glu Met Tyr Trp Val Ser Gly Ala Lys Ser Asn Thr Ile Lys Ser
           2740                2745                2750

Val Ser Thr Thr Ser Gln Leu Leu Leu Gly Arg Met Asp Gly Pro Arg
       2755                2760                2765

Arg Pro Val Lys Tyr Glu Glu Asp Val Asn Leu Gly Ser Gly Thr Arg
   2770                2775                2780

Ala Val Val Ser Cys Ala Glu Ala Pro Asn Met Lys Ile Ile Gly Asn
2785                2790                2795                2800

Arg Ile Glu Arg Ile Arg Ser Glu His Ala Glu Thr Trp Phe Phe Asp
               2805                2810                2815

Glu Asn His Pro Tyr Arg Thr Trp Ala Tyr His Gly Ser Tyr Glu Ala
           2820                2825                2830

Pro Thr Gln Gly Ser Ala Ser Ser Leu Ile Asn Gly Val Val Arg Leu
       2835                2840                2845

Leu Ser Lys Pro Trp Asp Val Val Thr Gly Val Thr Gly Ile Ala Met
   2850                2855                2860

Thr Asp Thr Thr Pro Tyr Gly Gln Gln Arg Val Phe Lys Glu Lys Val
2865                2870                2875                2880

Asp Thr Arg Val Pro Asp Pro Gln Glu Gly Thr Arg Gln Val Met Ser
               2885                2890                2895

Met Val Ser Ser Trp Leu Trp Lys Glu Leu Gly Lys His Lys Arg Pro
           2900                2905                2910

Arg Val Cys Thr Lys Glu Glu Phe Ile Asn Lys Val Arg Ser Asn Ala
       2915                2920                2925

Ala Leu Gly Ala Ile Phe Glu Glu Glu Lys Glu Trp Lys Thr Ala Val
   2930                2935                2940

Glu Ala Val Asn Asp Pro Arg Phe Trp Ala Leu Val Asp Lys Glu Arg
2945                2950                2955                2960

Glu His His Leu Arg Gly Glu Cys Gln Ser Cys Val Tyr Asn Met Met
               2965                2970                2975

Gly Lys Arg Glu Lys Lys Gln Gly Glu Phe Gly Lys Ala Lys Gly Ser
           2980                2985                2990

Arg Ala Ile Trp Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu Phe Glu
       2995                3000                3005

Ala Leu Gly Phe Leu Asn Glu Asp His Trp Met Gly Arg Glu Asn Ser
   3010                3015                3020

Gly Gly Gly Val Glu Gly Leu Gly Leu Gln Arg Leu Gly Tyr Val Leu
3025                3030                3035                3040

Glu Glu Met Ser Arg Ile Pro Gly Gly Arg Met Tyr Ala Asp Asp Thr
               3045                3050                3055

Ala Gly Trp Asp Thr Arg Ile Ser Arg Phe Asp Leu Glu Asn Glu Ala
           3060                3065                3070

Leu Ile Thr Asn Gln Met Glu Lys Gly His Arg Ala Leu Ala Leu Ala
       3075                3080                3085

Ile Ile Lys Tyr Thr Tyr Gln Asn Lys Val Val Lys Val Leu Arg Pro
   3090                3095                3100

Ala Glu Lys Gly Lys Thr Val Met Asp Ile Ile Ser Arg Gln Asp Gln
3105                3110                3115                3120

Arg Gly Ser Gly Gln Val Val Thr Tyr Ala Leu Asn Thr Phe Thr Asn
               3125                3130                3135

Leu Val Val Gln Leu Ile Arg Asn Met Glu Ala Glu Glu Val Leu Glu
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          3140                3145                3150

Met Gln Asp Leu Trp Leu Leu Arg Arg Ser Glu Lys Val Thr Asn Trp
       3155                3160                3165

Leu Gln Ser Asn Gly Trp Asp Arg Leu Lys Arg Met Ala Val Ser Gly
   3170                3175                3180

Asp Asp Cys Val Val Lys Pro Ile Asp Asp Arg Phe Ala His Ala Leu
3185                3190                3195                3200

Arg Phe Leu Asn Asp Met Gly Lys Val Arg Lys Asp Thr Gln Glu Trp
               3205                3210                3215

Lys Pro Ser Thr Gly Trp Asp Asn Trp Glu Glu Val Pro Phe Cys Ser
           3220                3225                3230

His His Phe Asn Lys Leu His Leu Lys Asp Gly Arg Ser Ile Val Val
       3235                3240                3245

Pro Cys Arg His Gln Asp Glu Leu Ile Gly Arg Ala Arg Val Ser Pro
   3250                3255                3260

Gly Ala Gly Trp Ser Ile Arg Glu Thr Ala Cys Leu Ala Lys Ser Tyr
3265                3270                3275                3280

Ala Gln Met Trp Gln Leu Leu Tyr Phe His Arg Arg Asp Leu Arg Leu
               3285                3290                3295

Met Ala Asn Ala Ile Cys Ser Ser Val Pro Val Asp Trp Val Pro Thr
           3300                3305                3310

Gly Arg Thr Thr Trp Ser Ile His Gly Lys Gly Glu Trp Met Thr Thr
       3315                3320                3325

Glu Asp Met Leu Val Val Trp Asn Arg Val Trp Ile Glu Glu Asn Asp
   3330                3335                3340

His Met Glu Asp Lys Thr Pro Val Thr Lys Trp Thr Asp Ile Pro Tyr
3345                3350                3355                3360

Leu Gly Lys Arg Glu Asp Leu Trp Cys Gly Ser Leu Ile Gly His Arg
               3365                3370                3375

Pro Arg Thr Thr Trp Ala Glu Asn Ile Lys Asn Thr Val Asn Met Met
           3380                3385                3390

Arg Arg Ile Ile Gly Asp Glu Glu Lys Tyr Val Asp Tyr Leu Ser Thr
       3395                3400                3405

Gln Val Arg Tyr Leu Gly Glu Glu Gly Ser Thr Pro Gly Val Leu
   3410                3415                3420


<210> SEQ ID NO 8
<211> LENGTH: 3423
<212> TYPE: PRT
<213> ORGANISM: Zika virus

<400> SEQUENCE: 8

Met Lys Asn Pro Lys Lys Lys Ser Gly Gly Phe Arg Ile Val Asn Met
 1               5                  10                  15

Leu Lys Arg Gly Val Ala Arg Val Ser Pro Phe Gly Gly Leu Lys Arg
            20                  25                  30

Leu Pro Ala Gly Leu Leu Leu Gly His Gly Pro Ile Arg Met Val Leu
        35                  40                  45

Ala Ile Leu Ala Phe Leu Arg Phe Thr Ala Ile Lys Pro Ser Leu Gly
    50                  55                  60

Leu Ile Asn Arg Trp Gly Ser Val Gly Lys Lys Glu Ala Met Glu Ile
65                  70                  75                  80
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Ile Lys Lys Phe Lys Lys Asp Leu Ala Ala Met Leu Arg Ile Ile Asn
                85                  90                  95

Ala Arg Lys Glu Lys Lys Arg Arg Gly Ala Asp Thr Asn Val Gly Ile
            100                 105                 110

Val Gly Leu Leu Leu Thr Thr Ala Met Ala Ala Glu Val Thr Arg Arg
        115                 120                 125

Gly Ser Ala Tyr Tyr Met Tyr Leu Asp Arg Asn Asp Ala Gly Glu Ala
    130                 135                 140

Ile Ser Phe Pro Thr Thr Leu Gly Met Asn Lys Cys Tyr Ile Gln Ile
145                 150                 155                 160

Met Asp Leu Gly His Met Cys Asp Ala Thr Met Ser Tyr Glu Cys Pro
                165                 170                 175

Met Leu Asp Glu Gly Val Glu Pro Asp Asp Val Asp Cys Trp Cys Asn
            180                 185                 190

Thr Thr Ser Thr Trp Val Val Tyr Gly Thr Cys His His Lys Lys Gly
        195                 200                 205

Glu Ala Arg Arg Ser Arg Arg Ala Val Thr Leu Pro Ser His Ser Thr
    210                 215                 220

Arg Lys Leu Gln Thr Arg Ser Gln Thr Trp Leu Glu Ser Arg Glu Tyr
225                 230                 235                 240

Thr Lys His Leu Ile Arg Val Glu Asn Trp Ile Phe Arg Asn Pro Gly
                245                 250                 255

Phe Ala Leu Ala Ala Ala Ala Ile Ala Trp Leu Leu Gly Ser Ser Thr
            260                 265                 270

Ser Gln Lys Val Ile Tyr Leu Val Met Ile Leu Leu Ile Ala Pro Ala
        275                 280                 285

Tyr Ser Ile Arg Cys Ile Gly Val Ser Asn Arg Asp Phe Val Glu Gly
    290                 295                 300

Met Ser Gly Gly Thr Trp Val Asp Val Val Leu Glu His Gly Gly Cys
305                 310                 315                 320

Val Thr Val Met Ala Gln Asp Lys Pro Thr Val Asp Ile Glu Leu Val
                325                 330                 335

Thr Thr Thr Val Ser Asn Met Ala Glu Val Arg Ser Tyr Cys Tyr Glu
            340                 345                 350

Ala Ser Ile Ser Asp Met Ala Ser Asp Ser Arg Cys Pro Thr Gln Gly
        355                 360                 365

Glu Ala Tyr Leu Asp Lys Gln Ser Asp Thr Gln Tyr Val Cys Lys Arg
    370                 375                 380

Thr Leu Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly Lys
385                 390                 395                 400

Gly Ser Leu Val Thr Cys Ala Lys Phe Ala Cys Ser Lys Lys Met Thr
                405                 410                 415

Gly Lys Ser Ile Gln Pro Glu Asn Leu Glu Tyr Arg Ile Met Leu Ser
            420                 425                 430

Val His Gly Ser Gln His Ser Gly Met Ile Val Asn Asp Thr Gly His
        435                 440                 445

Glu Thr Asp Glu Asn Arg Ala Lys Val Glu Ile Thr Pro Asn Ser Pro
    450                 455                 460

Arg Ala Glu Ala Thr Leu Gly Gly Phe Gly Ser Leu Gly Leu Asp Cys
465                 470                 475                 480

Glu Pro Arg Thr Gly Leu Asp Phe Ser Asp Leu Tyr Tyr Leu Thr Met
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               485                 490                 495

Asn Asn Lys His Trp Leu Val His Lys Glu Trp Phe His Asp Ile Pro
            500                 505                 510

Leu Pro Trp His Ala Gly Ala Asp Thr Gly Thr Pro His Trp Asn Asn
        515                 520                 525

Lys Glu Ala Leu Val Glu Phe Lys Asp Ala His Ala Lys Arg Gln Thr
    530                 535                 540

Val Val Val Leu Gly Ser Gln Glu Gly Ala Val His Thr Ala Leu Ala
545                 550                 555                 560

Gly Ala Leu Glu Ala Glu Met Asp Gly Ala Lys Gly Arg Leu Ser Ser
                565                 570                 575

Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Arg Leu Lys Gly
            580                 585                 590

Val Ser Tyr Ser Leu Cys Thr Ala Ala Phe Thr Phe Thr Lys Ile Pro
        595                 600                 605

Ala Glu Thr Leu His Gly Thr Val Thr Val Glu Val Gln Tyr Ala Gly
    610                 615                 620

Thr Asp Gly Pro Cys Lys Val Pro Ala Gln Met Ala Val Asp Met Gln
625                 630                 635                 640

Thr Leu Thr Pro Val Gly Arg Leu Ile Thr Ala Asn Pro Val Ile Thr
                645                 650                 655

Glu Ser Thr Glu Asn Ser Lys Met Met Leu Glu Leu Asp Pro Pro Phe
            660                 665                 670

Gly Asp Ser Tyr Ile Val Ile Gly Val Gly Glu Lys Lys Ile Thr His
        675                 680                 685

His Trp His Arg Ser Gly Ser Thr Ile Gly Lys Ala Phe Glu Ala Thr
    690                 695                 700

Val Arg Gly Ala Arg Arg Met Ala Val Leu Gly Asp Thr Ala Trp Asp
705                 710                 715                 720

Phe Gly Ser Val Gly Gly Ala Leu Asn Ser Leu Gly Lys Gly Ile His
                725                 730                 735

Gln Ile Phe Gly Ala Ala Phe Lys Ser Leu Phe Gly Gly Met Ser Trp
            740                 745                 750

Phe Ser Gln Ile Leu Ile Gly Thr Leu Leu Met Trp Leu Gly Leu Asn
        755                 760                 765

Thr Lys Asn Gly Ser Ile Ser Leu Met Cys Leu Ala Leu Gly Gly Val
    770                 775                 780

Leu Ile Phe Leu Ser Thr Ala Val Ser Ala Asp Val Gly Cys Ser Val
785                 790                 795                 800

Asp Phe Ser Lys Lys Glu Thr Arg Cys Gly Thr Gly Val Phe Val Tyr
                805                 810                 815

Asn Asp Val Glu Ala Trp Arg Asp Arg Tyr Lys Tyr His Pro Asp Ser
            820                 825                 830

Pro Arg Arg Leu Ala Ala Ala Val Lys Gln Ala Trp Glu Asp Gly Ile
        835                 840                 845

Cys Gly Ile Ser Ser Val Ser Arg Met Glu Asn Ile Met Trp Arg Ser
    850                 855                 860

Val Glu Gly Glu Leu Asn Ala Ile Leu Glu Glu Asn Gly Val Gln Leu
865                 870                 875                 880

Thr Val Val Val Gly Ser Val Lys Asn Pro Met Trp Arg Gly Pro Gln
                885                 890                 895
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Arg Leu Pro Val Pro Val Asn Glu Leu Pro His Gly Trp Lys Ala Trp
            900                 905                 910

Gly Lys Ser Tyr Phe Val Arg Ala Ala Lys Thr Asn Asn Ser Phe Val
        915                 920                 925

Val Asp Gly Asp Thr Leu Lys Glu Cys Pro Leu Lys His Arg Ala Trp
    930                 935                 940

Asn Ser Phe Leu Val Glu Asp His Gly Phe Gly Val Phe His Thr Ser
945                 950                 955                 960

Val Trp Leu Lys Val Arg Glu Asp Tyr Ser Leu Glu Cys Asp Pro Ala
                965                 970                 975

Val Ile Gly Thr Ala Val Lys Gly Lys Glu Ala Val His Ser Asp Leu
            980                 985                 990

Gly Tyr Trp Ile Glu Ser Glu Lys Asn Asp Thr Trp Arg Leu Lys Arg
        995                 1000                1005

Ala His Leu Ile Glu Met Lys Thr Cys Glu Trp Pro Lys Ser His Thr
    1010                1015                1020

Leu Trp Thr Asp Gly Ile Glu Glu Ser Asp Leu Ile Ile Pro Lys Ser
1025                1030                1035                1040

Leu Ala Gly Pro Leu Ser His His Asn Thr Arg Glu Gly Tyr Arg Thr
                1045                1050                1055

Gln Met Lys Gly Pro Trp His Ser Glu Glu Leu Glu Ile Arg Phe Glu
            1060                1065                1070

Glu Cys Pro Gly Thr Lys Val His Val Glu Glu Thr Cys Gly Thr Arg
        1075                1080                1085

Gly Pro Ser Leu Arg Ser Thr Thr Ala Ser Gly Arg Val Ile Glu Glu
    1090                1095                1100

Trp Cys Cys Arg Glu Cys Thr Met Pro Pro Leu Ser Phe Gln Ala Lys
1105                1110                1115                1120

Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Arg Lys Glu Pro Glu
                1125                1130                1135

Ser Asn Leu Val Arg Ser Met Val Thr Ala Gly Ser Thr Asp His Met
            1140                1145                1150

Asp His Phe Ser Leu Gly Val Leu Val Ile Leu Leu Met Val Gln Glu
        1155                1160                1165

Gly Leu Lys Lys Arg Met Thr Thr Lys Ile Ile Ile Ser Thr Ser Met
    1170                1175                1180

Ala Val Leu Val Ala Met Ile Leu Gly Gly Phe Ser Met Ser Asp Leu
1185                1190                1195                1200

Ala Lys Leu Ala Ile Leu Met Gly Ala Thr Phe Ala Glu Met Asn Thr
                1205                1210                1215

Gly Gly Asp Val Ala His Leu Ala Leu Ile Ala Ala Phe Lys Val Arg
            1220                1225                1230

Pro Ala Leu Leu Val Ser Phe Ile Phe Arg Ala Asn Trp Thr Pro Arg
        1235                1240                1245

Glu Ser Met Leu Leu Ala Leu Ala Ser Cys Leu Leu Gln Thr Ala Ile
    1250                1255                1260

Ser Ala Leu Glu Gly Asp Leu Met Val Leu Ile Asn Gly Phe Ala Leu
1265                1270                1275                1280

Ala Trp Leu Ala Ile Arg Ala Met Val Val Pro Arg Thr Asp Asn Ile
                1285                1290                1295
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Thr Leu Ala Ile Leu Ala Ala Leu Thr Pro Leu Ala Arg Gly Thr Leu
          1300                1305                1310

Leu Val Ala Trp Arg Ala Gly Leu Ala Thr Cys Gly Gly Phe Met Leu
       1315                1320                1325

Leu Ser Leu Lys Gly Lys Gly Ser Val Lys Lys Asn Leu Pro Phe Val
   1330                1335                1340

Met Ala Leu Gly Leu Thr Ala Val Arg Leu Val Asp Pro Ile Asn Val
1345                1350                1355                1360

Val Gly Leu Leu Leu Leu Thr Arg Ser Gly Lys Arg Ser Trp Pro Pro
               1365                1370                1375

Ser Glu Val Leu Thr Ala Val Gly Leu Ile Cys Ala Leu Ala Gly Gly
          1380                1385                1390

Phe Ala Lys Ala Asp Ile Glu Met Ala Gly Pro Met Ala Ala Val Gly
       1395                1400                1405

Leu Leu Ile Val Ser Tyr Val Val Ser Gly Lys Ser Val Asp Met Tyr
   1410                1415                1420

Ile Glu Arg Ala Gly Asp Ile Thr Trp Glu Lys Asp Ala Glu Val Thr
1425                1430                1435                1440

Gly Asn Ser Pro Arg Leu Asp Val Ala Leu Asp Glu Ser Gly Asp Phe
               1445                1450                1455

Ser Leu Val Glu Asp Asp Gly Pro Pro Met Arg Glu Ile Ile Leu Lys
          1460                1465                1470

Val Val Leu Met Thr Ile Cys Gly Met Asn Pro Ile Ala Ile Pro Phe
       1475                1480                1485

Ala Ala Gly Ala Trp Tyr Val Tyr Val Lys Thr Gly Lys Arg Ser Gly
   1490                1495                1500

Ala Leu Trp Asp Val Pro Ala Pro Lys Glu Val Lys Lys Gly Glu Thr
1505                1510                1515                1520

Thr Asp Gly Val Tyr Arg Val Met Thr Arg Arg Leu Leu Gly Ser Thr
               1525                1530                1535

Gln Val Gly Val Gly Val Met Gln Glu Gly Val Phe His Thr Met Trp
          1540                1545                1550

His Val Thr Lys Gly Ser Ala Leu Arg Ser Gly Glu Gly Arg Leu Asp
       1555                1560                1565

Pro Tyr Trp Gly Asp Val Lys Gln Asp Leu Val Ser Tyr Cys Gly Pro
   1570                1575                1580

Trp Lys Leu Asp Ala Ala Trp Asp Gly His Ser Glu Val Gln Leu Leu
1585                1590                1595                1600

Ala Val Pro Pro Gly Glu Arg Ala Arg Asn Ile Gln Thr Leu Pro Gly
               1605                1610                1615

Ile Phe Lys Thr Lys Asp Gly Asp Ile Gly Ala Val Ala Leu Asp Tyr
          1620                1625                1630

Pro Ala Gly Thr Ser Gly Ser Pro Ile Leu Asp Lys Cys Gly Arg Val
       1635                1640                1645

Ile Gly Leu Tyr Gly Asn Gly Val Val Ile Lys Asn Gly Ser Tyr Val
   1650                1655                1660

Ser Ala Ile Thr Gln Gly Arg Arg Glu Glu Glu Thr Pro Val Glu Cys
1665                1670                1675                1680

Phe Glu Pro Ser Met Leu Lys Lys Lys Gln Leu Thr Val Leu Asp Leu
               1685                1690                1695

His Pro Gly Ala Gly Lys Thr Arg Arg Val Leu Pro Glu Ile Val Arg
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          1700                1705                1710

Glu Ala Ile Lys Thr Arg Leu Arg Thr Val Ile Leu Ala Pro Thr Arg
       1715                1720                1725

Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu Pro Val Arg
   1730                1735                1740

Tyr Met Thr Thr Ala Val Asn Val Thr His Ser Gly Thr Glu Ile Val
1745                1750                1755                1760

Asp Leu Met Cys His Ala Thr Phe Thr Ser Arg Leu Leu Gln Pro Ile
               1765                1770                1775

Arg Val Pro Asn Tyr Asn Leu Tyr Ile Met Asp Glu Ala His Phe Thr
           1780                1785                1790

Asp Pro Ser Ser Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Glu
       1795                1800                1805

Met Gly Glu Ala Ala Ala Ile Phe Met Thr Ala Thr Pro Pro Gly Thr
   1810                1815                1820

Arg Asp Ala Phe Pro Asp Ser Asn Ser Pro Ile Met Asp Thr Glu Val
1825                1830                1835                1840

Glu Val Pro Glu Arg Ala Trp Ser Ser Gly Phe Asp Trp Val Thr Asp
               1845                1850                1855

His Ser Gly Lys Thr Val Trp Phe Val Pro Ser Val Arg Asn Gly Asn
           1860                1865                1870

Glu Ile Ala Ala Cys Leu Thr Lys Ala Gly Lys Arg Val Ile Gln Leu
       1875                1880                1885

Ser Arg Lys Thr Phe Glu Thr Glu Phe Gln Lys Thr Lys His Gln Glu
   1890                1895                1900

Trp Asp Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe
1905                1910                1915                1920

Lys Ala Asp Arg Val Ile Asp Ser Arg Arg Cys Leu Lys Pro Val Ile
               1925                1930                1935

Leu Asp Gly Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr His
           1940                1945                1950

Ala Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro Asn Lys
       1955                1960                1965

Pro Gly Asp Glu Tyr Leu Tyr Gly Gly Gly Cys Ala Glu Thr Asp Glu
   1970                1975                1980

Asp His Ala His Trp Leu Glu Ala Arg Met Leu Leu Asp Asn Ile Tyr
1985                1990                1995                2000

Leu Gln Asp Gly Leu Ile Ala Ser Leu Tyr Arg Pro Glu Ala Asp Lys
               2005                2010                2015

Val Ala Ala Ile Glu Gly Glu Phe Lys Leu Arg Thr Glu Gln Arg Lys
           2020                2025                2030

Thr Phe Val Glu Leu Met Lys Arg Gly Asp Leu Pro Val Trp Leu Ala
       2035                2040                2045

Tyr Gln Val Ala Ser Ala Gly Ile Thr Tyr Thr Asp Arg Arg Trp Cys
   2050                2055                2060

Phe Asp Gly Thr Thr Asn Asn Thr Ile Met Glu Asp Ser Val Pro Ala
2065                2070                2075                2080

Glu Val Trp Thr Arg His Gly Glu Lys Arg Val Leu Lys Pro Arg Trp
               2085                2090                2095

Met Asp Ala Arg Val Cys Ser Asp His Ala Ala Leu Lys Ser Phe Lys
           2100                2105                2110
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Glu Phe Ala Ala Gly Lys Arg Gly Ala Ala Phe Gly Val Met Glu Ala
       2115                2120                2125

Leu Gly Thr Leu Pro Gly His Met Thr Glu Arg Phe Gln Glu Ala Ile
   2130                2135                2140

Asp Asn Leu Ala Val Leu Met Arg Ala Glu Thr Gly Ser Arg Pro Tyr
2145                2150                2155                2160

Lys Ala Ala Ala Ala Gln Leu Pro Glu Thr Leu Glu Thr Ile Met Leu
               2165                2170                2175

Leu Gly Leu Leu Gly Thr Val Ser Leu Gly Ile Phe Phe Val Leu Met
           2180                2185                2190

Arg Asn Lys Gly Ile Gly Lys Met Gly Phe Gly Met Val Thr Leu Gly
       2195                2200                2205

Ala Ser Ala Trp Leu Met Trp Leu Ser Glu Ile Glu Pro Ala Arg Ile
   2210                2215                2220

Ala Cys Val Leu Ile Val Val Phe Leu Leu Leu Val Val Leu Ile Pro
2225                2230                2235                2240

Glu Pro Glu Lys Gln Arg Ser Pro Gln Asp Asn Gln Met Ala Ile Ile
               2245                2250                2255

Ile Met Val Ala Val Gly Leu Leu Gly Leu Ile Thr Ala Asn Glu Leu
           2260                2265                2270

Gly Trp Leu Glu Arg Thr Lys Ser Asp Leu Ser His Leu Met Gly Arg
       2275                2280                2285

Arg Glu Glu Gly Ala Thr Ile Gly Phe Ser Met Asp Ile Asp Leu Arg
   2290                2295                2300

Pro Ala Ser Ala Trp Ala Ile Tyr Ala Ala Leu Thr Thr Phe Ile Thr
2305                2310                2315                2320

Pro Ala Val Gln His Ala Val Thr Thr Ser Tyr Asn Asn Tyr Ser Leu
               2325                2330                2335

Met Ala Met Ala Thr Gln Ala Gly Val Leu Phe Gly Met Gly Lys Gly
           2340                2345                2350

Met Pro Phe Tyr Ala Trp Asp Phe Gly Val Pro Leu Leu Met Ile Gly
       2355                2360                2365

Cys Tyr Ser Gln Leu Thr Pro Leu Thr Leu Ile Val Ala Ile Ile Leu
   2370                2375                2380

Leu Val Ala His Tyr Met Tyr Leu Ile Pro Gly Leu Gln Ala Ala Ala
2385                2390                2395                2400

Ala Arg Ala Ala Gln Lys Arg Thr Ala Ala Gly Ile Met Lys Asn Pro
               2405                2410                2415

Val Val Asp Gly Ile Val Val Thr Asp Ile Asp Thr Met Thr Ile Asp
           2420                2425                2430

Pro Gln Val Glu Lys Lys Met Gly Gln Val Leu Leu Ile Ala Val Ala
       2435                2440                2445

Val Ser Ser Ala Ile Leu Ser Arg Thr Ala Trp Gly Trp Gly Glu Ala
   2450                2455                2460

Gly Ala Leu Ile Thr Ala Ala Thr Ser Thr Leu Trp Glu Gly Ser Pro
2465                2470                2475                2480

Asn Lys Tyr Trp Asn Ser Ser Thr Ala Thr Ser Leu Cys Asn Ile Phe
               2485                2490                2495

Arg Gly Ser Tyr Leu Ala Gly Ala Ser Leu Ile Tyr Thr Val Thr Arg
           2500                2505                2510
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Asn Ala Gly Leu Val Lys Arg Arg Gly Gly Gly Thr Gly Glu Thr Leu
       2515                2520                2525

Gly Glu Lys Trp Lys Ala Arg Leu Asn Gln Met Ser Ala Leu Glu Phe
   2530                2535                2540

Tyr Ser Tyr Lys Lys Ser Gly Ile Thr Glu Val Cys Arg Glu Glu Ala
2545                2550                2555                2560

Arg Arg Ala Leu Lys Asp Gly Val Ala Thr Gly Gly His Ala Val Ser
               2565                2570                2575

Arg Gly Ser Ala Lys Leu Arg Trp Leu Val Glu Arg Gly Tyr Leu Gln
           2580                2585                2590

Pro Tyr Gly Lys Val Ile Asp Leu Gly Cys Gly Arg Gly Gly Trp Ser
       2595                2600                2605

Tyr Tyr Ala Ala Thr Ile Arg Lys Val Gln Glu Val Lys Gly Tyr Thr
   2610                2615                2620

Lys Gly Gly Pro Gly His Glu Glu Pro Met Leu Val Gln Ser Tyr Gly
2625                2630                2635                2640

Trp Asn Ile Val Arg Leu Lys Ser Gly Val Asp Val Phe His Met Ala
               2645                2650                2655

Ala Glu Pro Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Ser
           2660                2665                2670

Ser Pro Glu Val Glu Glu Ala Arg Thr Leu Arg Val Leu Ser Met Val
       2675                2680                2685

Gly Asp Trp Leu Glu Lys Arg Pro Gly Ala Phe Cys Ile Lys Val Leu
   2690                2695                2700

Cys Pro Tyr Thr Ser Thr Met Met Glu Thr Leu Glu Arg Leu Gln Arg
2705                2710                2715                2720

Arg Tyr Gly Gly Gly Leu Val Arg Val Pro Leu Ser Arg Asn Ser Thr
               2725                2730                2735

His Glu Met Tyr Trp Val Ser Gly Ala Lys Ser Asn Thr Ile Lys Ser
           2740                2745                2750

Val Ser Thr Thr Ser Gln Leu Leu Leu Gly Arg Met Asp Gly Pro Arg
       2755                2760                2765

Arg Pro Val Lys Tyr Glu Glu Asp Val Asn Leu Gly Ser Gly Thr Arg
   2770                2775                2780

Ala Val Val Ser Cys Ala Glu Ala Pro Asn Met Lys Ile Ile Gly Asn
2785                2790                2795                2800

Arg Ile Glu Arg Ile Arg Ser Glu His Ala Glu Thr Trp Phe Phe Asp
               2805                2810                2815

Glu Asn His Pro Tyr Arg Thr Trp Ala Tyr His Gly Ser Tyr Glu Ala
           2820                2825                2830

Pro Thr Gln Gly Ser Ala Ser Ser Leu Ile Asn Gly Val Val Arg Leu
       2835                2840                2845

Leu Ser Lys Pro Trp Asp Val Val Thr Gly Val Thr Gly Ile Ala Met
   2850                2855                2860

Thr Asp Thr Thr Pro Tyr Gly Gln Gln Arg Val Phe Lys Glu Lys Val
2865                2870                2875                2880

Asp Thr Arg Val Pro Asp Pro Gln Glu Gly Thr Arg Gln Val Met Ser
               2885                2890                2895

Met Val Ser Ser Trp Leu Trp Lys Glu Leu Gly Lys His Lys Arg Pro
           2900                2905                2910

Arg Val Cys Thr Lys Glu Glu Phe Ile Asn Lys Val Arg Ser Asn Ala
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      2915                2920                2925

Ala Leu Gly Ala Ile Phe Glu Glu Glu Lys Glu Trp Lys Thr Ala Val
   2930                2935                2940

Glu Ala Val Asn Asp Pro Arg Phe Trp Ala Leu Val Asp Lys Glu Arg
2945                2950                2955                2960

Glu His His Leu Arg Gly Glu Cys Gln Ser Cys Val Tyr Asn Met Met
                2965                2970                2975

Gly Lys Arg Glu Lys Lys Gln Gly Glu Phe Gly Lys Ala Lys Gly Ser
           2980                2985                2990

Arg Ala Ile Trp Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu Phe Glu
      2995                3000                3005

Ala Leu Gly Phe Leu Asn Glu Asp His Trp Met Gly Arg Glu Asn Ser
   3010                3015                3020

Gly Gly Gly Val Glu Gly Leu Gly Leu Gln Arg Leu Gly Tyr Val Leu
3025                3030                3035                3040

Glu Glu Met Ser Arg Ile Pro Gly Gly Arg Met Tyr Ala Asp Asp Thr
                3045                3050                3055

Ala Gly Trp Asp Thr Arg Ile Ser Arg Phe Asp Leu Glu Asn Glu Ala
           3060                3065                3070

Leu Ile Thr Asn Gln Met Glu Lys Gly His Arg Ala Leu Ala Leu Ala
      3075                3080                3085

Ile Ile Lys Tyr Thr Tyr Gln Asn Lys Val Val Lys Val Leu Arg Pro
   3090                3095                3100

Ala Glu Lys Gly Lys Thr Val Met Asp Ile Ile Ser Arg Gln Asp Gln
3105                3110                3115                3120

Arg Gly Ser Gly Gln Val Val Thr Tyr Ala Leu Asn Thr Phe Thr Asn
                3125                3130                3135

Leu Val Val Gln Leu Ile Arg Ser Met Glu Ala Glu Glu Val Leu Glu
           3140                3145                3150

Met Gln Asp Leu Trp Leu Leu Arg Arg Ser Glu Lys Val Thr Asn Trp
      3155                3160                3165

Leu Gln Ser Asn Gly Trp Asp Arg Leu Lys Arg Met Ala Val Ser Gly
   3170                3175                3180

Asp Asp Cys Val Val Arg Pro Ile Asp Asp Arg Phe Ala His Ala Leu
3185                3190                3195                3200

Arg Phe Leu Asn Asp Met Gly Lys Val Arg Lys Asp Thr Gln Glu Trp
                3205                3210                3215

Lys Pro Ser Thr Gly Trp Asp Asn Trp Glu Glu Val Pro Phe Cys Ser
           3220                3225                3230

His His Phe Asn Lys Leu His Leu Lys Asp Gly Arg Ser Ile Val Val
      3235                3240                3245

Pro Cys Arg His Gln Asp Glu Leu Ile Gly Arg Ala Arg Val Ser Pro
   3250                3255                3260

Gly Ala Gly Trp Ser Ile Arg Glu Thr Ala Cys Leu Ala Lys Ser Tyr
3265                3270                3275                3280

Ala Gln Met Trp Gln Leu Leu Tyr Phe His Arg Arg Asp Leu Arg Leu
                3285                3290                3295

Met Ala Asn Ala Ile Cys Ser Ser Val Pro Val Asp Trp Val Pro Thr
           3300                3305                3310

Gly Arg Thr Thr Trp Ser Ile His Gly Lys Gly Glu Trp Met Thr Thr
      3315                3320                3325
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Glu Asp Met Leu Val Val Trp Asn Arg Val Trp Ile Glu Glu Asn Asp
   3330                3335                3340

His Met Glu Asp Lys Thr Pro Val Thr Lys Trp Thr Asp Ile Pro Tyr
3345                3350                3355                3360

Leu Gly Lys Arg Glu Asp Leu Trp Cys Gly Ser Leu Ile Gly His Arg
               3365                3370                3375

Pro Arg Thr Thr Trp Ala Glu Asn Ile Lys Asn Thr Val Asn Met Val
          3380                3385                3390

Arg Arg Ile Ile Gly Asp Glu Glu Lys Tyr Met Asp Tyr Leu Ser Thr
       3395                3400                3405

Gln Val Arg Tyr Leu Gly Glu Glu Gly Ser Thr Pro Gly Val Leu
   3410                3415                3420


<210> SEQ ID NO 9
<211> LENGTH: 3423
<212> TYPE: PRT
<213> ORGANISM: Zika virus

<400> SEQUENCE: 9

Met Lys Asn Pro Lys Lys Lys Ser Gly Gly Phe Arg Ile Val Asn Met
 1               5                  10                  15

Leu Lys Arg Gly Val Ala Arg Val Ser Pro Phe Gly Gly Leu Lys Arg
            20                  25                  30

Leu Pro Ala Gly Leu Leu Leu Gly His Gly Pro Ile Arg Met Val Leu
        35                  40                  45

Ala Ile Leu Ala Phe Leu Arg Phe Thr Ala Ile Lys Pro Ser Leu Gly
    50                  55                  60

Leu Ile Asn Arg Trp Gly Ser Val Gly Lys Lys Glu Ala Met Glu Ile
65                  70                  75                  80

Ile Lys Lys Phe Lys Lys Asp Leu Ala Ala Met Leu Arg Ile Ile Asn
                85                  90                  95

Ala Arg Lys Glu Lys Lys Arg Arg Gly Ala Asp Thr Ser Val Gly Ile
            100                 105                 110

Val Gly Leu Leu Leu Thr Thr Ala Met Ala Ala Glu Val Thr Arg Arg
        115                 120                 125

Gly Ser Ala Tyr Tyr Met Tyr Leu Asp Arg Asn Asp Ala Gly Glu Ala
    130                 135                 140

Ile Ser Phe Pro Thr Thr Leu Gly Met Asn Lys Cys Tyr Ile Gln Ile
145                 150                 155                 160

Met Asp Leu Gly His Met Cys Asp Ala Thr Met Ser Tyr Glu Cys Pro
                165                 170                 175

Met Leu Asp Glu Gly Val Glu Pro Asp Asp Val Asp Cys Trp Cys Asn
            180                 185                 190

Thr Thr Ser Thr Trp Val Val Tyr Gly Thr Cys His His Lys Lys Gly
        195                 200                 205

Glu Ala Arg Arg Ser Arg Arg Ala Val Thr Leu Pro Ser His Ser Thr
    210                 215                 220

Arg Lys Leu Gln Thr Arg Ser Gln Thr Trp Leu Glu Ser Arg Glu Tyr
225                 230                 235                 240

Thr Lys His Leu Ile Arg Val Glu Asn Trp Ile Phe Arg Asn Pro Gly
                245                 250                 255

Phe Ala Leu Ala Ala Ala Ala Ile Ala Trp Leu Leu Gly Ser Ser Thr
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            260                 265                 270

Ser Gln Lys Val Ile Tyr Leu Val Met Ile Leu Leu Ile Ala Pro Ala
        275                 280                 285

Tyr Ser Ile Arg Cys Ile Gly Val Ser Asn Arg Asp Phe Val Glu Gly
    290                 295                 300

Met Ser Gly Gly Thr Trp Val Asp Val Val Leu Glu His Gly Gly Cys
305                 310                 315                 320

Val Thr Val Met Ala Gln Asp Lys Pro Thr Val Asp Ile Glu Leu Val
                325                 330                 335

Thr Thr Thr Val Ser Asn Met Ala Glu Val Arg Ser Tyr Cys Tyr Glu
            340                 345                 350

Ala Ser Ile Ser Asp Met Ala Ser Asp Ser Arg Cys Pro Thr Gln Gly
        355                 360                 365

Glu Ala Tyr Leu Asp Lys Gln Ser Asp Thr Gln Tyr Val Cys Lys Arg
    370                 375                 380

Thr Leu Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly Lys
385                 390                 395                 400

Gly Ser Leu Val Thr Cys Ala Lys Phe Ala Cys Ser Lys Lys Met Thr
                405                 410                 415

Gly Lys Ser Ile Gln Pro Glu Asn Leu Glu Tyr Arg Ile Met Leu Ser
            420                 425                 430

Val His Gly Ser Gln His Ser Gly Met Ile Val Asn Asp Thr Gly His
        435                 440                 445

Glu Thr Asp Glu Asn Arg Ala Lys Val Glu Ile Thr Pro Asn Ser Pro
    450                 455                 460

Arg Ala Glu Ala Thr Leu Gly Gly Phe Gly Ser Leu Gly Leu Asp Cys
465                 470                 475                 480

Glu Pro Arg Thr Gly Leu Asp Phe Ser Asp Leu Tyr Tyr Leu Thr Met
                485                 490                 495

Asn Asn Lys His Trp Leu Val His Lys Glu Trp Phe His Asp Ile Pro
            500                 505                 510

Leu Pro Trp His Ala Gly Ala Asp Thr Gly Thr Pro His Trp Asn Asn
        515                 520                 525

Lys Glu Ala Leu Val Glu Phe Lys Asp Ala His Ala Lys Arg Gln Thr
    530                 535                 540

Val Val Val Leu Gly Ser Gln Glu Gly Ala Val His Thr Ala Leu Ala
545                 550                 555                 560

Gly Ala Leu Glu Ala Glu Met Asp Gly Ala Lys Gly Arg Leu Ser Ser
                565                 570                 575

Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Arg Leu Lys Gly
            580                 585                 590

Val Ser Tyr Ser Leu Cys Thr Ala Ala Phe Thr Phe Thr Lys Ile Pro
        595                 600                 605

Ala Glu Thr Leu His Gly Thr Val Thr Val Glu Val Gln Tyr Ala Gly
    610                 615                 620

Thr Asp Gly Pro Cys Lys Val Pro Ala Gln Met Ala Val Asp Met Gln
625                 630                 635                 640

Thr Leu Thr Pro Val Gly Arg Leu Ile Thr Ala Asn Pro Val Ile Thr
                645                 650                 655

Glu Ser Thr Glu Asn Ser Lys Met Met Leu Glu Leu Asp Pro Pro Phe
            660                 665                 670
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Gly Asp Ser Tyr Ile Val Ile Gly Val Gly Glu Lys Lys Ile Thr His
        675                 680                 685

His Trp His Arg Ser Gly Ser Thr Ile Gly Lys Ala Phe Glu Ala Thr
    690                 695                 700

Val Arg Gly Ala Lys Arg Met Ala Val Leu Gly Asp Thr Ala Trp Asp
705                 710                 715                 720

Phe Gly Ser Val Gly Gly Ala Leu Asn Ser Leu Gly Lys Gly Ile His
                725                 730                 735

Gln Ile Phe Gly Ala Ala Phe Lys Ser Leu Phe Gly Gly Met Ser Trp
            740                 745                 750

Phe Ser Gln Ile Leu Ile Gly Thr Leu Leu Met Trp Leu Gly Leu Asn
        755                 760                 765

Thr Lys Asn Gly Ser Ile Ser Leu Met Cys Leu Ala Leu Gly Gly Val
    770                 775                 780

Leu Ile Phe Leu Ser Thr Ala Val Ser Ala Asp Val Gly Cys Ser Val
785                 790                 795                 800

Asp Phe Ser Lys Lys Glu Thr Arg Cys Gly Thr Gly Val Phe Val Tyr
                805                 810                 815

Asn Asp Val Glu Ala Trp Arg Asp Arg Tyr Lys Tyr His Pro Asp Ser
            820                 825                 830

Pro Arg Arg Leu Ala Ala Ala Val Lys Gln Ala Trp Glu Asp Gly Ile
        835                 840                 845

Cys Gly Ile Ser Ser Val Ser Arg Met Glu Asn Ile Met Trp Arg Ser
    850                 855                 860

Val Glu Gly Glu Leu Asn Ala Ile Leu Glu Glu Asn Gly Val Gln Leu
865                 870                 875                 880

Thr Val Val Val Gly Ser Val Lys Asn Pro Met Trp Arg Gly Pro Gln
                885                 890                 895

Arg Leu Pro Val Pro Val Asn Glu Leu Pro His Gly Trp Lys Ala Trp
            900                 905                 910

Gly Lys Ser Tyr Phe Val Arg Ala Ala Lys Thr Asn Asn Ser Phe Val
        915                 920                 925

Val Asp Gly Asp Thr Leu Lys Glu Cys Pro Leu Lys His Arg Ala Trp
    930                 935                 940

Asn Ser Phe Leu Val Glu Asp His Gly Phe Gly Val Phe His Thr Ser
945                 950                 955                 960

Val Trp Leu Lys Val Arg Glu Asp Tyr Ser Leu Glu Cys Asp Pro Ala
                965                 970                 975

Val Ile Gly Thr Ala Val Lys Gly Lys Glu Ala Val His Ser Asp Leu
            980                 985                 990

Gly Tyr Trp Ile Glu Ser Glu Lys Asn Asp Thr Trp Arg Leu Lys Arg
        995                 1000                1005

Ala His Leu Ile Glu Met Lys Thr Cys Glu Trp Pro Lys Ser His Thr
   1010                1015                1020

Leu Trp Thr Asp Gly Ile Glu Glu Ser Asp Leu Ile Ile Pro Lys Ser
1025                1030                1035                1040

Leu Ala Gly Pro Leu Ser His His Asn Thr Arg Glu Gly Tyr Arg Thr
               1045                1050                1055

Gln Met Lys Gly Pro Trp His Ser Glu Glu Leu Glu Ile Arg Phe Glu
           1060                1065                1070
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Glu Cys Pro Gly Thr Lys Val His Val Glu Glu Thr Cys Gly Thr Arg
       1075                1080                1085

Gly Pro Ser Leu Arg Ser Thr Thr Ala Ser Gly Arg Val Ile Glu Glu
   1090                1095                1100

Trp Cys Cys Arg Glu Cys Thr Met Pro Pro Leu Ser Phe Arg Ala Lys
1105                1110                1115                1120

Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Arg Lys Glu Pro Glu
               1125                1130                1135

Ser Asn Leu Val Arg Ser Met Val Thr Ala Gly Ser Thr Asp His Met
           1140                1145                1150

Asp His Phe Ser Leu Gly Val Leu Val Ile Leu Leu Met Val Gln Glu
       1155                1160                1165

Gly Leu Lys Lys Arg Met Thr Thr Lys Ile Ile Ile Ser Thr Ser Met
   1170                1175                1180

Ala Val Leu Val Ala Met Ile Leu Gly Gly Phe Ser Met Ser Asp Leu
1185                1190                1195                1200

Ala Lys Leu Ala Ile Leu Met Gly Ala Thr Phe Ala Glu Met Asn Thr
               1205                1210                1215

Gly Gly Asp Val Ala His Leu Ala Leu Ile Ala Ala Phe Lys Val Arg
           1220                1225                1230

Pro Ala Leu Leu Val Ser Phe Ile Phe Arg Ala Asn Trp Thr Pro Arg
       1235                1240                1245

Glu Ser Met Leu Leu Ala Leu Ala Ser Cys Leu Leu Gln Thr Ala Ile
   1250                1255                1260

Ser Ala Leu Glu Gly Asp Leu Met Val Leu Ile Asn Gly Phe Ala Leu
1265                1270                1275                1280

Ala Trp Leu Ala Ile Arg Ala Met Val Val Pro Arg Thr Asp Asn Ile
               1285                1290                1295

Thr Leu Ala Ile Leu Ala Ala Leu Thr Pro Leu Ala Arg Gly Thr Leu
           1300                1305                1310

Leu Val Ala Trp Arg Ala Gly Leu Ala Thr Cys Gly Gly Phe Met Leu
       1315                1320                1325

Leu Ser Leu Lys Gly Lys Gly Ser Val Lys Lys Asn Leu Pro Phe Val
   1330                1335                1340

Met Ala Leu Gly Leu Thr Ala Val Arg Leu Val Asp Pro Ile Asn Val
1345                1350                1355                1360

Val Gly Leu Leu Leu Leu Thr Arg Ser Gly Lys Arg Ser Trp Pro Pro
               1365                1370                1375

Ser Glu Val Leu Thr Ala Val Gly Leu Ile Cys Ala Leu Ala Gly Gly
           1380                1385                1390

Phe Ala Lys Ala Asp Ile Glu Met Ala Gly Pro Met Ala Ala Val Gly
       1395                1400                1405

Leu Leu Ile Val Ser Tyr Val Val Ser Gly Lys Ser Val Asp Met Tyr
   1410                1415                1420

Ile Glu Arg Ala Gly Asp Ile Thr Trp Glu Lys Asp Ala Glu Val Thr
1425                1430                1435                1440

Gly Asn Ser Pro Arg Leu Asp Val Ala Leu Asp Glu Ser Gly Asp Phe
               1445                1450                1455

Ser Leu Val Glu Asp Asp Gly Pro Pro Met Arg Glu Ile Ile Leu Lys
           1460                1465                1470

Val Val Leu Met Thr Ile Cys Gly Met Asn Pro Ile Ala Ile Pro Phe
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      1475                1480                1485

Ala Ala Gly Ala Trp Tyr Val Tyr Val Lys Thr Gly Lys Arg Ser Gly
   1490                1495                1500

Ala Leu Trp Asp Val Pro Ala Pro Lys Glu Val Lys Lys Gly Glu Thr
1505                1510                1515                1520

Thr Asp Gly Val Tyr Arg Val Met Thr Arg Arg Leu Leu Gly Ser Thr
               1525                1530                1535

Gln Val Gly Val Gly Val Met Gln Glu Gly Val Phe His Thr Met Trp
           1540                1545                1550

His Val Thr Lys Gly Ser Ala Leu Arg Ser Gly Glu Gly Arg Leu Asp
      1555                1560                1565

Pro Tyr Trp Gly Asp Val Lys Gln Asp Leu Val Ser Tyr Cys Gly Pro
   1570                1575                1580

Trp Lys Leu Asp Ala Ala Trp Asp Gly His Ser Glu Val Gln Leu Leu
1585                1590                1595                1600

Ala Val Pro Pro Gly Glu Arg Ala Arg Asn Ile Gln Thr Leu Pro Gly
               1605                1610                1615

Ile Phe Lys Thr Lys Asp Gly Asp Ile Gly Ala Val Ala Leu Asp Tyr
           1620                1625                1630

Pro Ala Gly Thr Ser Gly Ser Pro Ile Leu Asp Lys Cys Gly Arg Val
      1635                1640                1645

Ile Gly Leu Tyr Gly Asn Gly Val Val Ile Lys Asn Gly Ser Tyr Val
   1650                1655                1660

Ser Ala Ile Thr Gln Gly Arg Arg Glu Glu Glu Thr Pro Val Glu Cys
1665                1670                1675                1680

Phe Glu Pro Ser Met Leu Lys Lys Lys Gln Leu Thr Val Leu Asp Leu
               1685                1690                1695

His Pro Gly Ala Gly Lys Thr Arg Arg Val Leu Pro Glu Ile Val Arg
           1700                1705                1710

Glu Ala Ile Lys Thr Arg Leu Arg Thr Val Ile Leu Ala Pro Thr Arg
      1715                1720                1725

Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu Pro Val Arg
   1730                1735                1740

Tyr Met Thr Thr Ala Val Asn Val Thr His Ser Gly Thr Glu Ile Val
1745                1750                1755                1760

Asp Leu Met Cys His Ala Thr Phe Thr Ser Arg Leu Leu Gln Pro Ile
               1765                1770                1775

Arg Val Pro Asn Tyr Asn Leu Tyr Ile Met Asp Glu Ala His Phe Thr
           1780                1785                1790

Asp Pro Ser Ser Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Glu
      1795                1800                1805

Met Gly Glu Ala Ala Ala Ile Phe Met Thr Ala Thr Pro Pro Gly Thr
   1810                1815                1820

Arg Asp Ala Phe Pro Asp Ser Asn Ser Pro Ile Met Asp Thr Glu Val
1825                1830                1835                1840

Glu Val Pro Glu Arg Ala Trp Ser Ser Gly Phe Asp Trp Val Thr Asp
               1845                1850                1855

His Ser Gly Lys Thr Val Trp Phe Val Pro Ser Val Arg Asn Gly Asn
           1860                1865                1870

Glu Ile Ala Ala Cys Leu Thr Lys Ala Gly Lys Arg Val Ile Gln Leu
      1875                1880                1885
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Ser Arg Lys Thr Phe Glu Thr Glu Phe Gln Lys Thr Lys His Gln Glu
   1890                1895                1900

Trp Asp Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe
1905                1910                1915                1920

Lys Ala Asp Arg Val Ile Asp Ser Arg Arg Cys Leu Lys Pro Val Ile
               1925                1930                1935

Leu Asp Gly Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr His
           1940                1945                1950

Ala Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro Asn Lys
       1955                1960                1965

Pro Gly Asp Glu Tyr Leu Tyr Gly Gly Gly Cys Ala Glu Thr Asp Glu
   1970                1975                1980

Asp His Ala His Trp Leu Glu Ala Arg Met Leu Leu Asp Asn Ile Tyr
1985                1990                1995                2000

Leu Gln Asp Gly Leu Ile Ala Ser Leu Tyr Arg Pro Glu Ala Asp Lys
               2005                2010                2015

Val Ala Ala Ile Glu Gly Glu Phe Lys Leu Arg Thr Glu Gln Arg Lys
           2020                2025                2030

Thr Phe Val Glu Leu Met Lys Arg Gly Asp Leu Pro Val Trp Leu Ala
       2035                2040                2045

Tyr Gln Val Ala Ser Ala Gly Ile Thr Tyr Thr Asp Arg Arg Trp Cys
   2050                2055                2060

Phe Asp Gly Thr Thr Asn Asn Thr Ile Met Glu Asp Ser Val Pro Ala
2065                2070                2075                2080

Glu Val Trp Thr Arg His Gly Glu Lys Arg Val Leu Lys Pro Arg Trp
               2085                2090                2095

Met Asp Ala Arg Val Cys Ser Asp His Ala Ala Leu Lys Ser Phe Lys
           2100                2105                2110

Glu Phe Ala Ala Gly Lys Arg Gly Ala Ala Phe Gly Val Met Glu Ala
       2115                2120                2125

Leu Gly Thr Leu Pro Gly His Met Thr Glu Arg Phe Gln Glu Ala Ile
   2130                2135                2140

Asp Asn Leu Ala Val Leu Met Arg Ala Glu Thr Gly Ser Arg Pro Tyr
2145                2150                2155                2160

Lys Ala Ala Ala Ala Gln Leu Pro Glu Thr Leu Glu Thr Ile Met Leu
               2165                2170                2175

Leu Gly Leu Leu Gly Thr Val Ser Leu Gly Ile Phe Phe Val Leu Met
           2180                2185                2190

Arg Asn Lys Gly Ile Gly Lys Met Gly Phe Gly Met Val Thr Leu Gly
       2195                2200                2205

Ala Ser Ala Trp Leu Met Trp Leu Ser Glu Ile Glu Pro Ala Arg Ile
   2210                2215                2220

Ala Cys Val Leu Ile Val Val Phe Leu Leu Leu Val Val Leu Ile Pro
2225                2230                2235                2240

Glu Pro Glu Lys Gln Arg Ser Pro Gln Asp Asn Gln Met Ala Ile Ile
               2245                2250                2255

Ile Met Val Ala Val Gly Leu Leu Gly Leu Ile Thr Ala Asn Glu Leu
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Gly Trp Leu Glu Arg Thr Lys Ser Asp Leu Ser His Leu Met Gly Arg
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Pro Ala Val Gln His Ala Val Thr Thr Ser Tyr Asn Asn Tyr Ser Leu
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Met Ala Met Ala Thr Gln Ala Gly Val Leu Phe Gly Met Gly Lys Gly
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Met Pro Phe Tyr Ala Trp Asp Phe Gly Val Pro Leu Leu Met Ile Gly
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Cys Tyr Ser Gln Leu Thr Pro Leu Thr Leu Ile Val Ala Ile Ile Leu
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Leu Val Ala His Tyr Met Tyr Leu Ile Pro Gly Leu Gln Ala Ala Ala
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Ala Arg Ala Ala Gln Lys Arg Thr Ala Ala Gly Ile Met Lys Asn Pro
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Val Val Asp Gly Ile Val Val Thr Asp Ile Asp Thr Met Thr Ile Asp
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Pro Gln Val Glu Lys Lys Met Gly Gln Val Leu Leu Ile Ala Val Ala
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Val Ser Ser Ala Ile Leu Ser Arg Thr Ala Trp Gly Trp Gly Glu Ala
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Gly Ala Leu Ile Thr Ala Ala Thr Ser Thr Leu Trp Glu Gly Ser Pro
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Asn Lys Tyr Trp Asn Ser Ser Thr Ala Thr Ser Leu Cys Asn Ile Phe
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Arg Gly Ser Tyr Leu Ala Gly Ala Ser Leu Ile Tyr Thr Val Thr Arg
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Asn Ala Gly Leu Val Lys Arg Arg Gly Gly Gly Thr Gly Glu Thr Leu
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Gly Glu Lys Trp Lys Ala Arg Leu Asn Gln Met Ser Ala Leu Glu Phe
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Tyr Ser Tyr Lys Lys Ser Gly Ile Thr Glu Val Cys Arg Glu Glu Ala
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Arg Arg Ala Leu Lys Asp Gly Val Ala Thr Gly Gly His Ala Val Ser
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Arg Gly Ser Ala Lys Leu Arg Trp Leu Val Glu Arg Gly Tyr Leu Gln
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Pro Tyr Gly Lys Val Ile Asp Leu Gly Cys Gly Arg Gly Gly Trp Ser
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Tyr Tyr Ala Ala Thr Ile Arg Lys Val Gln Glu Val Lys Gly Tyr Thr
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Lys Gly Gly Pro Gly His Glu Glu Pro Met Leu Val Gln Ser Tyr Gly
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Trp Asn Ile Val Arg Leu Lys Ser Gly Val Asp Val Phe His Met Ala
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Ala Glu Pro Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Ser
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Ser Pro Glu Val Glu Glu Ala Arg Thr Leu Arg Val Leu Ser Met Val
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Gly Asp Trp Leu Glu Lys Arg Pro Gly Ala Phe Cys Ile Lys Val Leu
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His Glu Met Tyr Trp Val Ser Gly Ala Lys Ser Asn Thr Ile Lys Ser
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Val Ser Thr Thr Ser Gln Leu Leu Leu Gly Arg Met Asp Gly Pro Arg
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Arg Pro Val Lys Tyr Glu Glu Asp Val Asn Leu Gly Ser Gly Thr Arg
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Ala Val Val Ser Cys Ala Glu Ala Pro Asn Met Lys Ile Ile Gly Asn
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Arg Ile Glu Arg Ile Arg Ser Glu His Ala Glu Thr Trp Phe Phe Asp
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Glu Asn His Pro Tyr Arg Thr Trp Ala Tyr His Gly Ser Tyr Glu Ala
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Leu Ser Lys Pro Trp Asp Val Val Thr Gly Val Thr Gly Ile Ala Met
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Thr Asp Thr Thr Pro Tyr Gly Gln Gln Arg Val Phe Lys Glu Lys Val
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Asp Thr Arg Val Pro Asp Pro Gln Glu Gly Thr Arg Gln Val Met Ser
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Ala Leu Gly Ala Ile Phe Glu Glu Glu Lys Glu Trp Lys Thr Ala Val
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Glu Ala Val Asn Asp Pro Arg Phe Trp Ala Leu Val Asp Lys Glu Arg
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Glu His His Leu Arg Gly Glu Cys Gln Ser Cys Val Tyr Asn Met Met
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Ala Leu Gly Phe Leu Asn Glu Asp His Trp Met Gly Arg Glu Asn Ser
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Leu Ile Thr Asn Gln Met Glu Lys Gly His Arg Ala Leu Ala Leu Ala
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Ile Ile Lys Tyr Thr Tyr Gln Asn Lys Val Val Lys Val Leu Arg Pro
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Asp Asp Cys Val Val Lys Pro Ile Asp Asp Arg Phe Ala His Ala Leu
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Arg Phe Leu Asn Asp Met Gly Lys Val Arg Lys Asp Thr Gln Glu Trp
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Lys Pro Ser Thr Gly Trp Asp Asn Trp Glu Glu Val Pro Phe Cys Ser
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His His Phe Asn Lys Leu His Leu Lys Asp Gly Arg Ser Ile Val Val
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Pro Cys Arg His Gln Asp Glu Leu Ile Gly Arg Ala Arg Val Ser Pro
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Gly Ala Gly Trp Ser Ile Arg Glu Thr Ala Cys Leu Ala Lys Ser Tyr
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Ala Gln Met Trp Gln Leu Leu Tyr Phe His Arg Arg Asp Leu Arg Leu
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Met Ala Asn Ala Ile Cys Ser Ser Val Pro Val Asp Trp Val Pro Thr
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Gly Arg Thr Thr Trp Ser Ile His Gly Lys Gly Glu Trp Met Thr Thr
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Glu Asp Met Leu Val Val Trp Asn Arg Val Trp Ile Glu Glu Asn Asp
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His Met Glu Asp Lys Thr Pro Val Thr Lys Trp Thr Asp Ile Pro Tyr
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Leu Gly Lys Arg Glu Asp Leu Trp Cys Gly Ser Leu Ile Gly His Arg
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Pro Arg Thr Thr Trp Ala Glu Asn Ile Lys Asn Thr Val Asn Met Val
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Arg Arg Ile Ile Gly Asp Glu Glu Lys Tyr Met Asp Tyr Leu Ser Thr
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Gln Val Arg Tyr Leu Gly Glu Glu Gly Ser Thr Pro Gly Val Leu
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<213> ORGANISM: Zika virus

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What is claimed is:

1. A recombinant nucleic acid vector comprising a heterologous promoter operably linked to a nucleotide sequence encoding flavivirus prM/E, which vector lacks nucleic acid sequences encoding one or more of flavivirus NS1, NS2A, NS2B NS3, NS4A NS4B or NS5 and optionally lacks nucleic acid sequences encoding functional flavivirus capsid.

2. The recombinant vector of claim **1** wherein the heterologous promoter is a heterologous viral promoter. The recombinant vector of claim **1** which includes a portion of flavivirus capsid sequences.

4. The recombinant vector of claim **1** wherein the capsid sequence includes amino acids 98 to 112 of the capsid protein encoded by SEQ ID NO:1 or a protein having at least 80% amino acid sequence identity thereto.

5. The recombinant vector of claim **1** wherein the flavivirus is a Zika virus.

6. The recombinant vector of claim **1** wherein the prM/E sequences have at least 80% amino acid sequence identity to the prM/E sequences encoded by any one of SEQ ID Nos. 1-3 or 5.

7. The recombinant vector of claim **1** wherein the prWE sequences are operably linked to a heterologous secretion signal.

8. The recombinant vector of claim **7** wherein the heterologous secretion signal is a TPA, IL-2, IgG kappa light chain, CD33, or Oikosin secretion signal.

9. A vaccine comprising an effective amount of a flavivirus like particle comprising a lipid bilayer comprising flavivirus prM/E but which particle lacks one or more of flavivirus NS1, NS2A, NS2B, NS3, NS4A, NS4B or NS5 and optionally lacks functional flavivirus capsid.

10. The vaccine of claim **9** further comprising one or more adjuvants.

11. The vaccine of claim **10** wherein the adjuvant comprises alum, monophosphoryl lipid A (MPLA), squalene, aluminum hydroxide absorbed TLR4 agonist, dimethyldioctadecylammonium, tripalmitoyl-S-glyceryl cysteine, trehalose dibehenate, saponin, MF59, AS03, virosomes, AS04, CpG, imidazoquinoline, poly I:C, flagellin, or any combination thereof

12. The vaccine of claim **9** wherein the flavivirus is a Zika virus.

13. The vaccine of claim **9** wherein the prM/E sequences have at least 80% amino acid sequence identity to the prM/E sequences encoded by any one of SEQ ID Nos. 1-3 or 5.

14. A method to prevent, inhibit or treat flavivirus infection in a mammal, comprising: administering to the mammal a composition comprising an effective amount of a flavivirus like particle comprising a lipid bilayer comprising flavivirus prM/E but which particle lacks one or more of flavivirus NS1, NS2A, NS2B, NS3, NS4A, NS4B or NSS and optionally lacks functional flavivirus capsid, or a composition comprising an effective amount of anti-flavivirus antibodies.

13. The method of claim **14** wherein the mammal is a female mammal.

14. The method of claim **14** wherein the mammal is a human.

15. The method of claim **14** wherein the flavivirus is a Zika virus.

16. The method of claim **17** wherein the prM/E sequences have at least 80% amino acid sequence identity to the prM/E sequences encoded by any one of SEQ ID Nos. 1-3 or 5.

17. The method of claim **14** wherein the composition comprising the flavivirus like particle is administered intramuscularly, subcutaneously or intranasally.

18. The method of claim **14** wherein the composition inhibits flavivirus infection.

19. The method of claim **14** wherein the composition treats flavivirus infection.

20. The method of claim **14** wherein the composition comprising antibodies comprises antibodies pooled from multiple donors that were infected with the flavivirus.

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