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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.

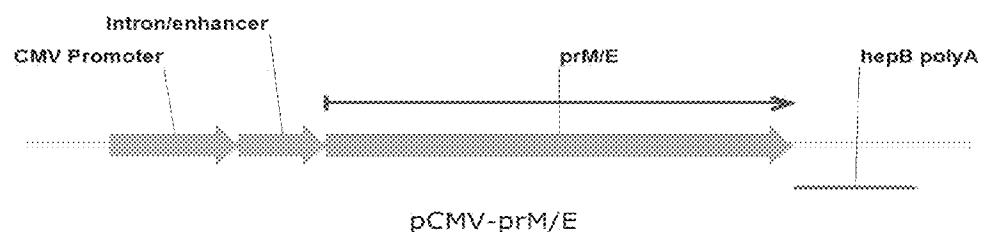


FIG. 1B.

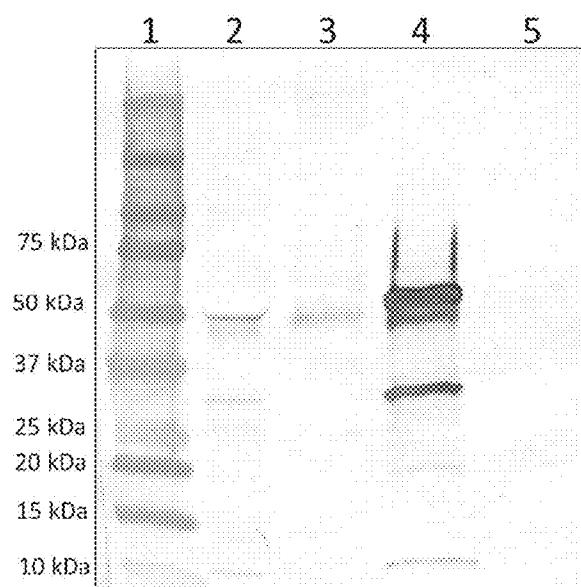


FIG. 1C.

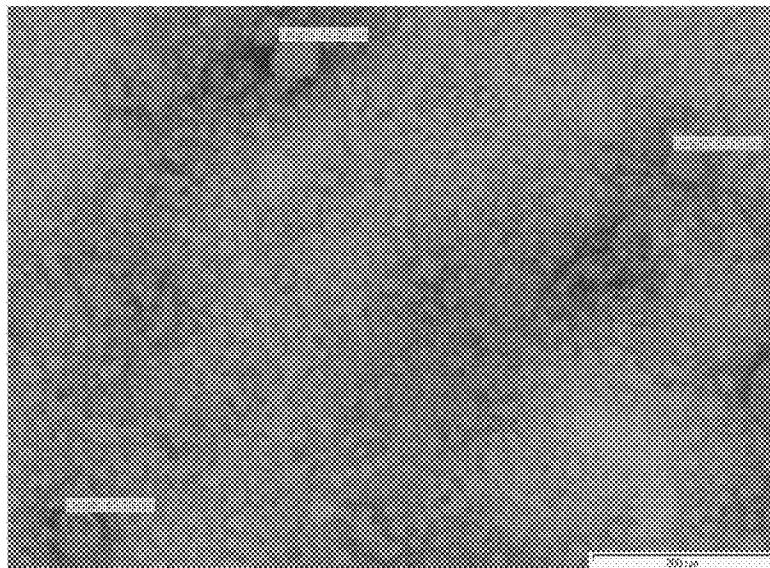


FIG. 1D.

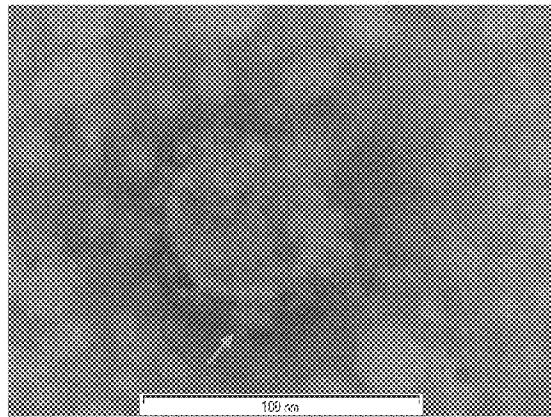


FIG. 1E.

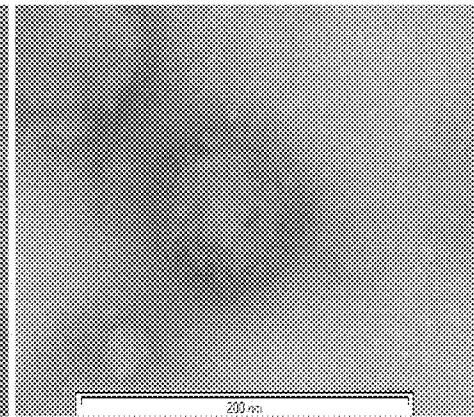


FIG. 2A.

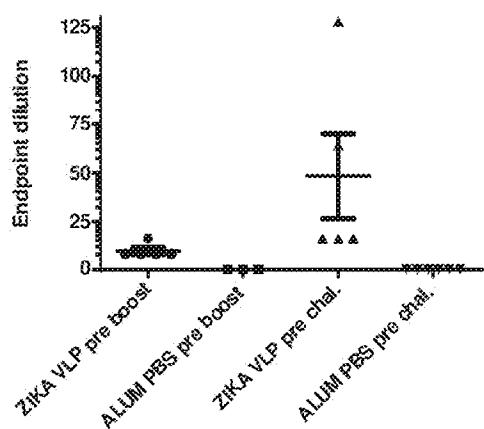


FIG. 2B.

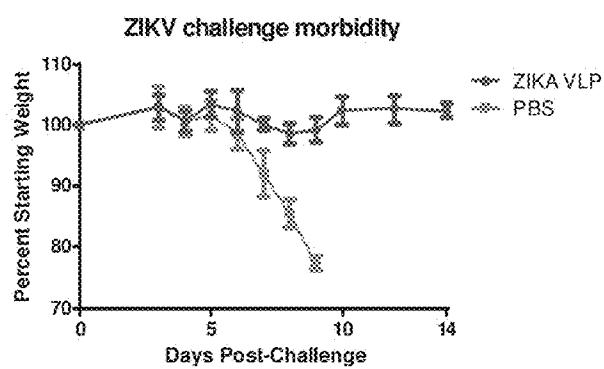


FIG. 2C.

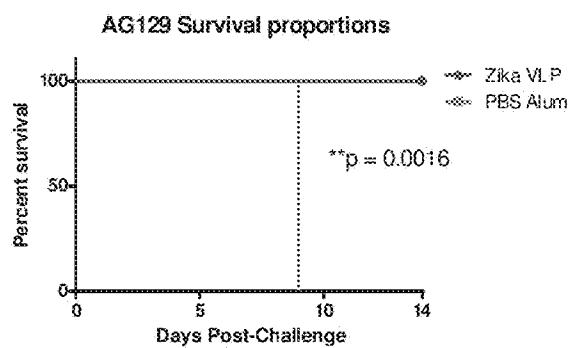


FIG. 2D.

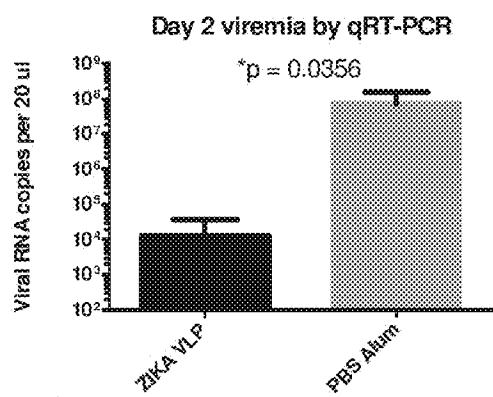


FIG. 2E.

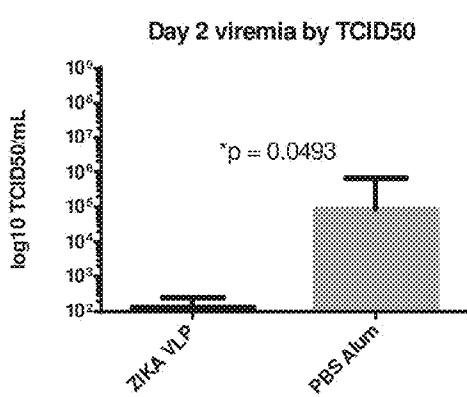


FIG. 2F.

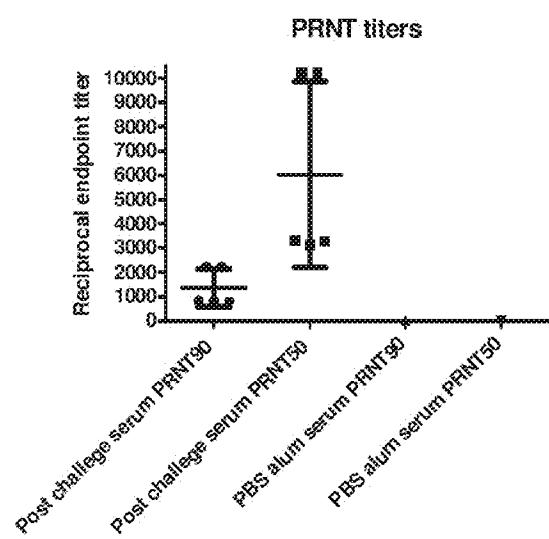


FIG. 3A.

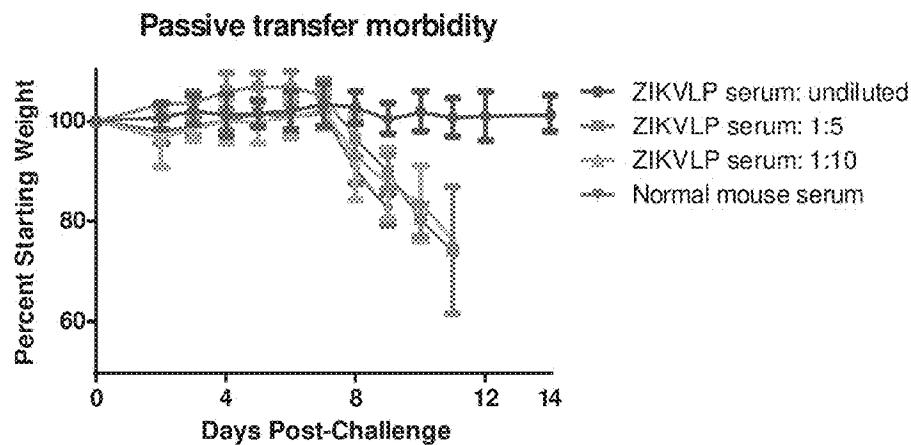


FIG. 3B.

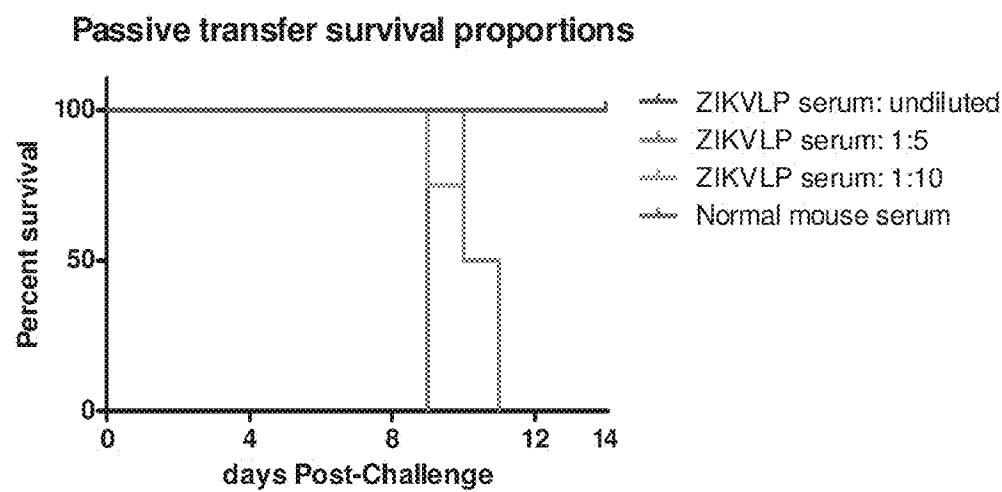


FIG. 4

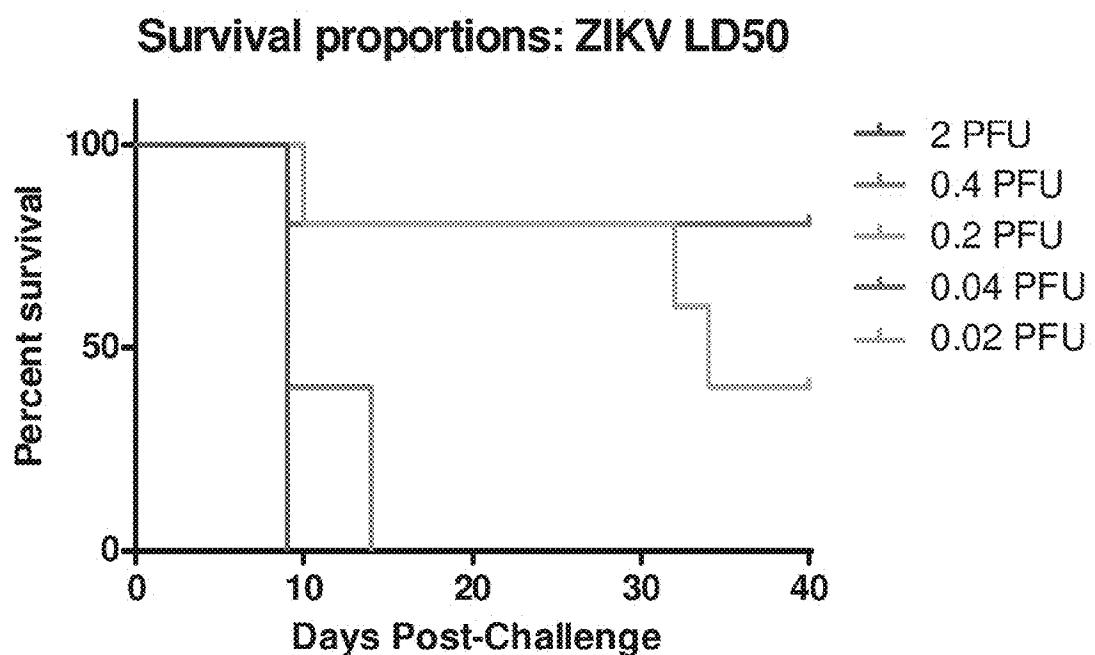


FIG. 5A

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

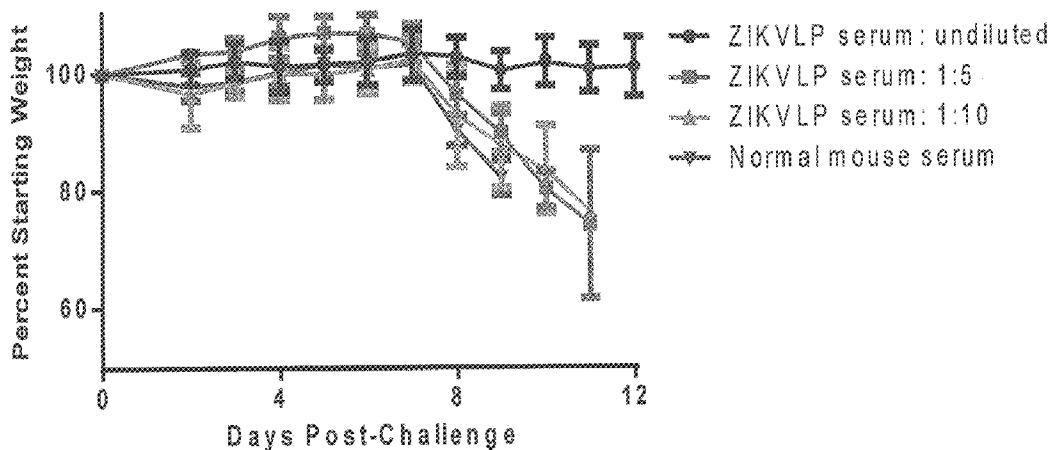
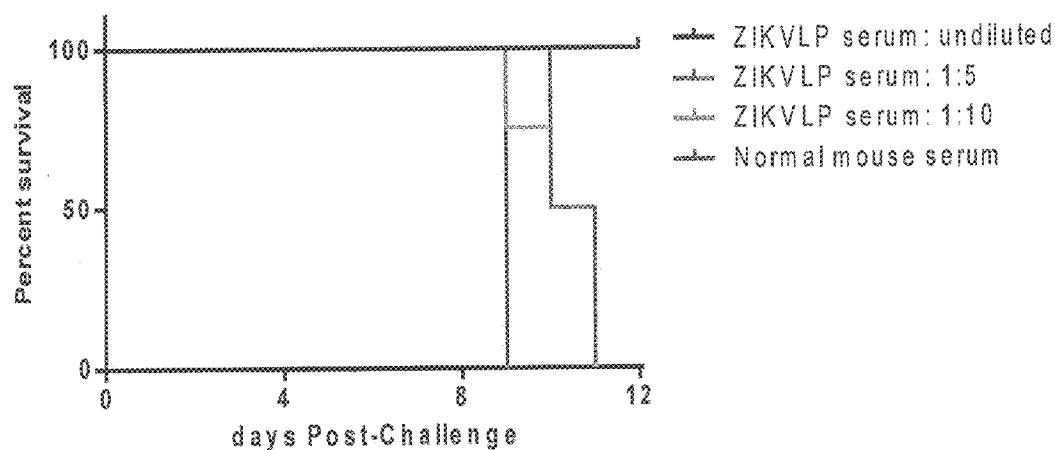


FIG. 5B

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



111 TGTGATACT CATACTCTTC CTITTTCTATA TTATTGAAGC ATTTATCAGG GTTATTGTCT CATGAGC
ACAACATGA GTATGAGAAG GAAAAAGTAT AATAACTTCG TAAATAGTCC CAATAACAGA GTACTCG
101 ANAANTNNGG GTTCCCCGCN CTTTNCCTCG AAAAGTGCCA CCTGACCTCG NCGGATCGGG AGATCTC
TNTTNNMCC CAAGGGGCGN GTAAANGGGC ITTTCACCGT GGACTSCAGC NGGCTAGCC C TCTAGAGC
201 GCTCTGATGC CGCATAGTIA AGCCAGTATC TGCTCCCTGC TTGTGTGTG GAGGTCGCTG AGTAGTGC
CGAGACTACG GGGTATCAAT TCGGTATAG ACCAGGGACG AACRCAUAC CTCAGCGAC TCATCAC
301 CTTGACCGAC AATTGCACTGA AGAATCTGCT TAGGTTAGG CGTTTGCGC TGCTTCGCGA TGTACGGC
GAACGGCTG TIAACGCTACT TCTTAGACGA ATCCCAATCC GCBAACAGCG AGGAAAGCGGT ACATGCC
401 AGTTATTAAT AGTAATCAAT TACGGGGTCA TTACTICATA GCCATATAT GGAGTTCCGC GTTACATI
TCAATAATTIA TCATTAGTTA ATGCCCCAGT AATCAAGTAT CGGTATATA CCTCAAGGGCG CAATGTA
501 CCAACGACCC CGGCCATIG AGGICAATAA TGACGTATGT TCCCAGTAGA AGGCGAATAG GGACTTT
GGTGTGGGG GGGCGCTAAC TGCAGTTATT ACTGCATACA AGGCTATCAT TGCGGTTATC CCTGAAA
601 BACTGCCAC TTGGCACTAC ATCAAGTGT A TCAATGCCA AGTCCGGCCC CTATGACGT CAATGAC
TTGACGGCTG AACCGICATG TAGTTCACAT ASTATACGGT TCAACGGGGG GATAACTSCA GTTACTG
~~~~~  
NcoI  
701 ATGACCTTAC GGGACTTTCC TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATIACC ATGGTGA  
TACTGGAATG CCCTGAAAGG ATGACCGTC ATGTAGATGC ATAATCAGTA GCGATAATGG TACCACT  
801 AGCGGTTGA CTCACGGGG A TTCCAAGTC TCCACCCAT TGACGTCAAT GGGAGTTGT TTTGGCA  
TCGCCAAACT GAGTCCCCCT AAAGGTTCAAG AGGTGGGGTA ACTECAGTTA CCCTCAAACA AAACCGTC  
901 TAACCCGGCC CGGTGACGC AAATGGGGGG TAGGCGTGTG CCGTGGGGAGG TCTATATAAG CAGAGCT  
ATTGGGGGGG GCGCAACTGCG TTTACCCGGC ATCCGACAT GCCACCCCTCC AGATATATIC GTCTCGA  
1001 CATCCACGCT GTTTGACCT CCATACAAGA CACCGGGGAC GATCCAGCT CCGGGGCCGG GAACGGT  
GTAGGTGCGA CAAAATCTGA GGTATCTCT GTGGCCCTGG CTAGGTGCGA GGCACCCGGCC CTTCGCA  
1101 ACTCACCGTC CGGATCTCAAG CAAGCAGGT A TGTACTCTCC AGGCTGGGGC TGGCTTCGGC AGTCAAG/  
TGACTGGCAG GCCTAGAGTC GTTCCCTCAT ACAIGAGAGG TCCCACCCGG ACCGAAGGGG TCAGTTC  
~~~~~  
BamHI
1201 CTCTTACATG TACCTTTGC TTGCTCAAC CCTGACTATC TTCCAGGTCA GGATCCCAGA GTCAGGG
GAGAATGTAC ATGGAARACG AACGGACTG GGACTGATAG AAGGTCAGT CCTAGGGTCT CAGTCCC
1301 GAACAGTAAA CCTGCTCCG AATATTGCT CTCACATCTC GTCAATCTCC GCGACGGACTG GGGACCC
CTTGTCAATT GGGACGAGG TTATAACCGA GAGTGTAGAG CAGTTAGAGG CGCTCCTGAC CCCTGGG/
1401 CCTCCTGCTG ACCACAGCTA TGGCAGCGGA GGTCACTAGA CGTGGGACTG CATACTATAT GTACTTG
GGAGGACGAC TGGTGTGGAT ACCGTGGCT CCAGTGTATCT GCACCCCTCAC GTATGATATA CATGAC
1501 CCAACCACAT TGGGGATCAA TAAGTGTAT ATACAGATCA TGGATCTTGG ACACATGTGT GATGCCAC
GGTGTGGTA ACCCCTACTT ATTACACAATA TATGTCTAGT ACCTAGAAC TGTGTACACA CTACGGT
1601 GGGTGGAACC AGATGACGTC GATGTTGGT GCAACACGAC GTCAACTTGG GTTGTGTACG GAACCTG
CCCACCTTGG TCTACTGCA CTAACAAACCA CGTTGTGCTG CAGTTGAACC CAACACATGC CTGGAC
1701 AAGAGCTGTG ACGCTCCCT CCCATTCCAC TAGGAACTG CAAACCCGT CGCAACACTG GTTGGAA
TTCTCGACAC TGGCAGGGGA GGGTAAGGTG ATCCCTGAC GTTGGCCCA GCGTTGGAC CAACCTT
1801 GAAAATTGGA TATTCAAGGA CCTGCTTC GCGTTAGAG CAGCTGCCAT CGCTTGGCTT TTGGGAA
CTTTAACCT ATAAGTCCTI GGCACCGAG CGCAATCTC GTGACGGTA CGGAACCGAA AACCTT
1901 TGATACTGCT GATTGCCCG GCATACAGCA TCAGGTGCA AGGAGTCAGC AATAGGGACT TTGTGGAA
ACTATGACGA CTAACGGGC CGTATGTGT AGTCCACCA TCCCTCACTCG TTATCCCTGA AACACCT
2001 CTTGGAACAT GGAGGTTGTG TCACCGTAAT GGCACAGGAC AAACCGACTG TCGACATAGA GCTGGT?
GAACCTTGTG CTCACACAG AGTGGCATT A CCGTGTCTG TTTGGCTGAC AGCTGTATCT CGACCAAC
2101 TCC TACTGCT ATGAGGCATC AATATCGAC ATGGCTTCGG ACAGCGCTG CCCAACACAA GGTGAAGC
AGGATGACGA TACTCCGTAG TTATAGCTG TACCGAAGCC TGTGGCCAC GGGTTGTGT CCACTTC
2201 TCTSCAAACG AACGTTAGT GACAGAGGT GGGAAATGG ATGTGGACTT TTTGGCAAAG GGAGCCT
AGACGTTTC TTGCAATCAC CTGTCTCCGA CCCCTTTAC TACACCTGAA AAACCGTTTC CCTCGGA

FIG. 6A

2301 AATGACCGGG AAGAGCATCC AGCCAGAGAA TCTGGAGTAC CGGATAATGC TGTCAAGTTCA TGGCTCC
 TTACTGGCCC TTCTCGTAGG TCGGTCTCTT AGACCTCATG GCCTATTACG ACAGTCAGT ACCGAGGK

2401 CATGAAACTG ATGAGAATAG AGCGAAGGTT GAGATAACGC CCAATTCAACC AAGAGCCGA CCCACCC
 GTACTTGCAC TACTCTTATC TCGCTTCCAA CTCTATTGCG GGTIAAGTGG TTCTCGGCTT CGGTGGGK

2501 AACCCAGGAC AGGCCTTGAC TTITCAGATT TGTATTACTT GACTATGAAT AACAAAGCACT CGTTGGGK
 TTGGCTCCTG TCAGGAACTG AAAAGTCTAA ACATAATGAA CTGATACTTA TTGTTCGTGA CCAACCAK

2601 TTGGCACGCT GGGGCAGACA CGCGAAGTCC ACACGTGGAAC AACAAAGAAG CACTGGTAGA GTTCAAG
 AACCGTCCGA CCCCGTGTGT GGCGTTGAGG TGTGACCTG TTGTTCTTC GTGACCATCT CAAGTICK

2701 CTAGGGAGTC AAGAAGGAGC AGTTCACACG GCCCTTGCTG GAGCTCIGGA GGCTGAGATG GATGGTICK
 GATCCCTCAG TTCTTCCTCG TCAAGTGTGC CGGGAAACGAC CTGAGACCT CCGACTCTAC CTACCAK

2801 GTCGGCTGAA AATGGATAAA CTTAGATTGA AGGGCGTGTCA ATACTCCTTG IGTACCGCAG CGTTCAK
 CAGGGACATT TTACCTAATT GAATCTAACT ICCCGCACAG TATGAGGAAC ACATGGCGTC GCAAGTICK

2901 GACAGTCACA GTGGAGGTAC AGTACCCAGG GACAGATGGA CCTTGCAAGG TTCCAGCTCA GATGGCCK
 CTGTCAGTGT CACCTCCATG TCAATGCGTGC CTGTCACCT GGAAACGTTCC AAGGTCGAGT CTACCGCK

3001 TTGATAACCG CTAACCCCGT AATCACTGAA ACCACTGAGA ACTCTAAGAT GATGCTGGAA CTTGATCK
 AACTATTGGC GATTGGGGCA TTAGTGACTT TCGTGACTCT TGAGATTCTA CTACGACCTT GAACTAGK

3101 TCGGGGAGAA GAAGATCACC CACCACTGGC ACAGGAGTGG CAGCACCATT GGAAAAGCAT TTGAAGCK
 AGCCCCCTCTT CTCTAGTGG GTGGTGACCG TGTCTCACC GTCTGGTAA CCTTTCTGA AACTTCGK

3201 GGGAGACACA GCCTGGGACT TTGGATCAGT TGGAGGGCT CTCAACTCAT TGGCAAGGG CATCCATK
 CCCTCTGTT CGGACCCCTGA AACCTAGTCA ACCTCCCGA GAGTTGAGTA ACCCGTCTCCC GTAGGTAK

3301 GGAGGAATGT CCTGGTTCTC ACAAAATTCTC ATIGGAACGT TGCTGATGTG GTGGGTCTG AACACAAK
 CCTCCCTACA GGACCAAGAG TGTAAAGAG TAACCTTGCA ACCACTACAC CAACCCAGAC TTGTTGK

3401 TAGGGGGAGT GTGATCTTC TTATCCACAG CTGTCCTGCG TGATGTGGGG TGCTCGGTGT GAGGATCK
 ATCCCCCTCA CAACTAGAAG AATAGGTGTC GACAGACAG ACTACACCCC ACGAGCCACA CTCCCTAGK

3501 CCCTAAACTT CATGGTTAC GTAAATGAA GTGGGGGAC ATTGCCACAA GATCATATTG TACAAAC
 GGGATTGAA GTACCCAATG CATTAAACCTT CAACCCCTG TAACGGTGT CTAGTATAAC ATGTTTCK

3601 CAGGCTTATT GATTGGAAAG TATGTCAAAG GATTGTGGGT CTTTGGGCT TTGCTGCTCC ATTTCAC
 GTCCGGATAA CTAACCTTTC ATACAGTTTC CTAACACCA GAAAACCCGA AACGACGAGG TAAATCTK

3701 GCATGTATAC AAGCTAAACA GGCTTCACT TTCTGCCAA CTTACAAGGC CTITCTAAGT AAACAGT
 CGTACATATG TTCGATTGT CCCAAACTGA AAGAGCGGTT GAATGTTCCG CAAAGATTCA TTGTCOK

3801 CTGGTCTGTG CCAAGTGTGTT GCTGACGCAA CCCCCACTGG CTGGGGCTTG GCCATAGGCC ATCACCGK
 GACCAGACAC GTTACACAAA CGACTGCGTT GGGGGTGACC GACCCCGAAC CGGTATCCGG TAGTCGK

3901 CCATACTGCG GAACTCTAG CGCTTGTGTT TGCTCGCAGG CGGTCTGGAS CAAAGCTCAT AGGAACCK
 GGTATGACGC CTGAGGAGTC GCGGAACAAA ACGAGGCTCG CCGAGACCTC GTTTCGAGTA TCCCTGAK

4001 TCGTTTCGAT CTACGTATGA TCTTTTCCC TCTGCAAAA ATTATGGGA CATCATGAAG CCCCCTGK
 AGCAAAGCTA GATGCATACT AGAAAAAGGG AGACGGTTT TAATACCCCT GTAGTACTTC GGGGAACCK

EcoRI

4101 TTTTCATTGC AATAGTGTGT TGGAAATTTC TGTGCTCTC ACTCGGAAGG AATTCCTGCAT TAATGAA
 AAAAGTAACG TTATCACACA ACCTTAAAAA ACACAGAGAG TGAGCCTTCC TTAAGACGTA ATTACTTCK

4201 TTGGGCGCTC TTCCGCTTCC TCGCTCACTG ANCTCGNTGC GCTTCGGTGC T
 AACCCGCGAG AAGGGGAAGG AGCGACTGAC TNGACCNACG CGAAGCCAGC A

FIG. 6B

pTriex4-neo Expression cassette

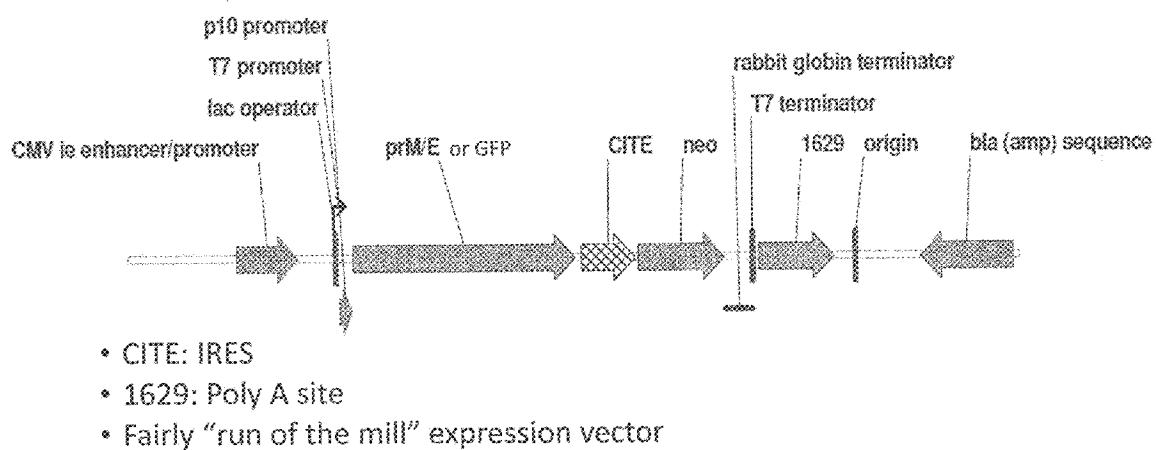


FIG. 7

pTriex4-neo GFP expression in HEK-293

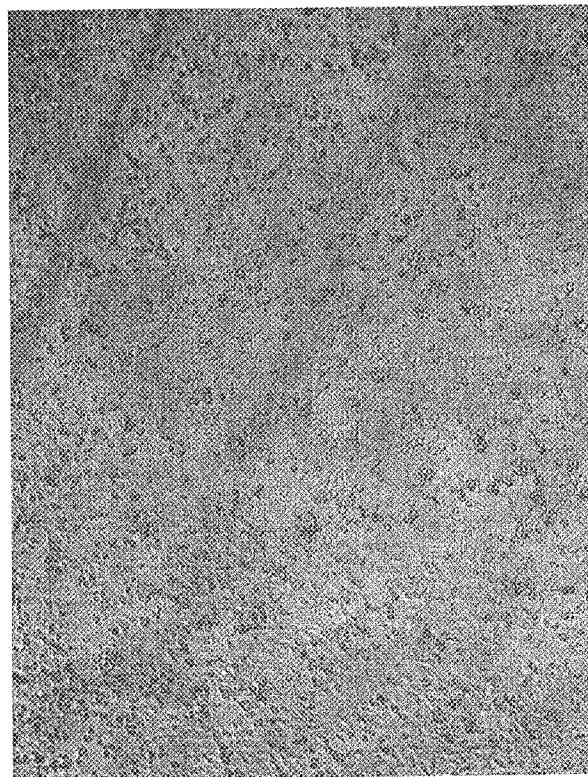
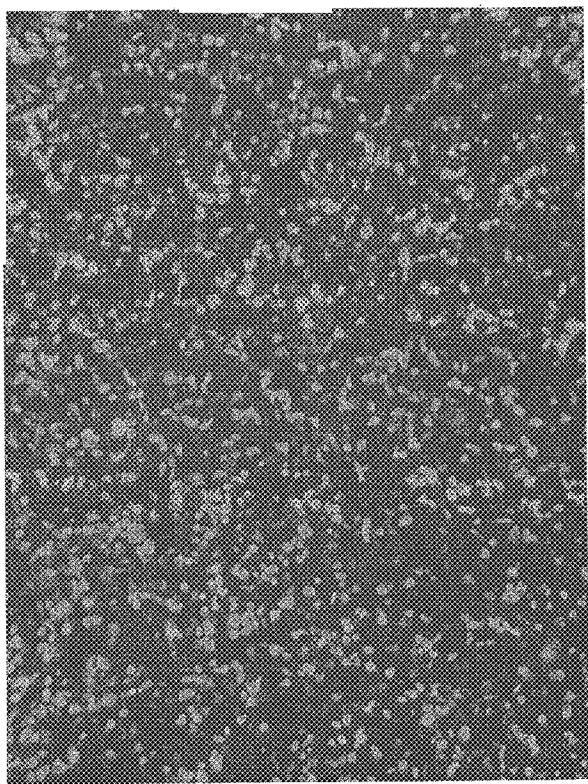


FIG. 8A

pcMV GFP expression in HEK-293

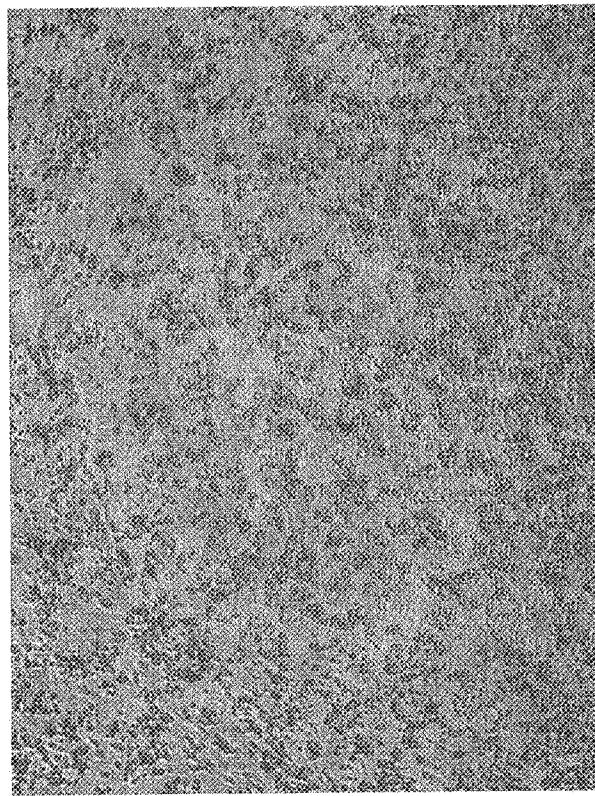
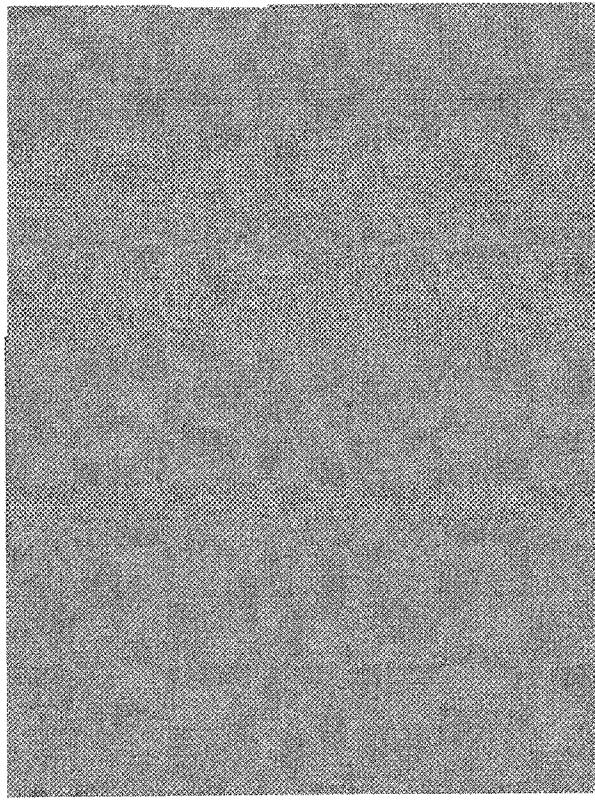
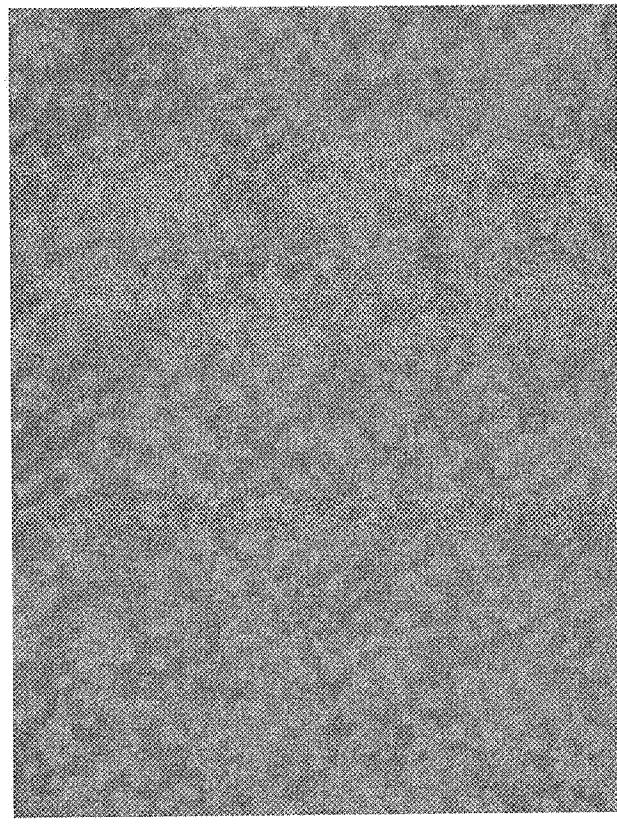


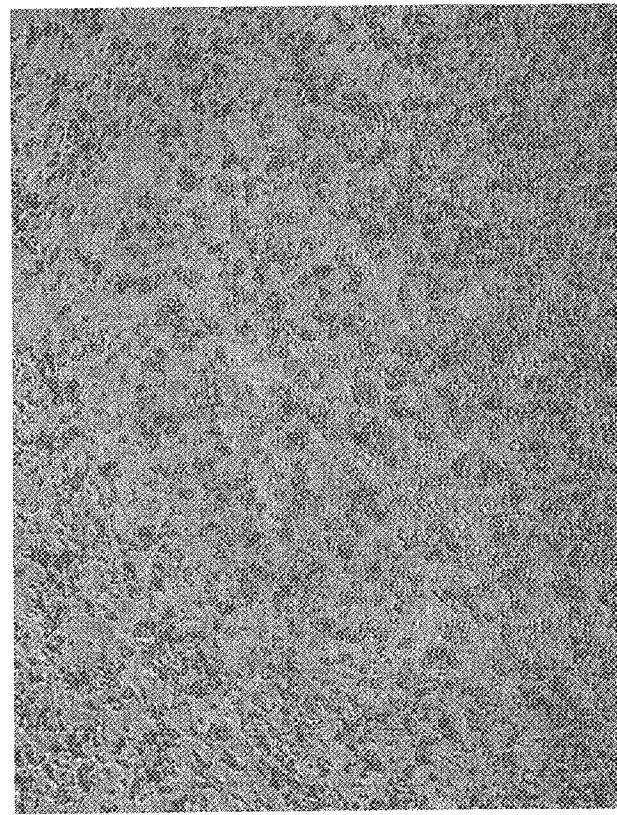
FIG. 8B

pCMV GFP expression in HEK-293



- Lamp turned down about 70%

FIG. 8C



pTriex vs pCMV prM/E expression

- 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

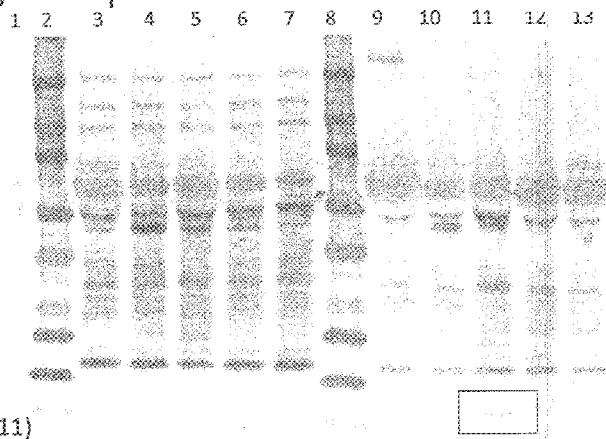


FIG. 9

Preliminary studies in mice

- Mice were injected IP with $\sim 10^6$ 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

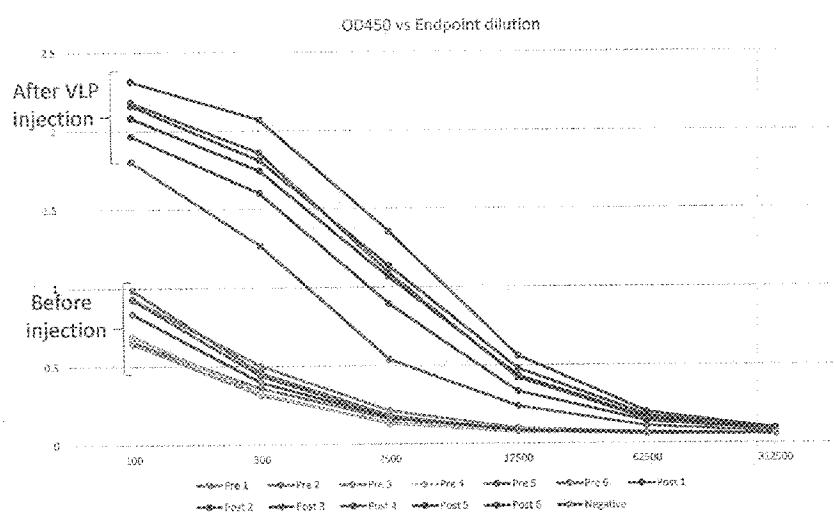
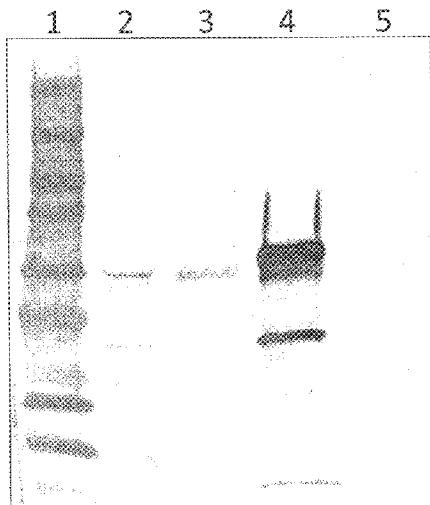


FIG. 10

Zika VLP purification: post sucrose purification Western blot

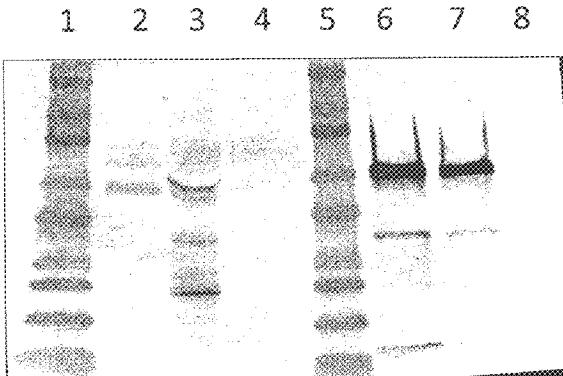


- 1: Marker
- 2: VLP 100,000g precipitation (previous slide)
- 3: Zika virus +
- 4: pCMV – Frnch-Poly post sucrose purification
- 5: pCMV-GFP post sucrose purification

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



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

	VLP+	IM	F (n=2) M (n=3)	12 (n=5)	2 µg total prossin	5
	Adjuvant	IM	F (n=2) M (n=3)	12 (n=5)	N/A	6

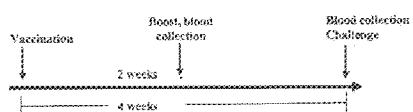


FIG. 14

Antibody two weeks post boost

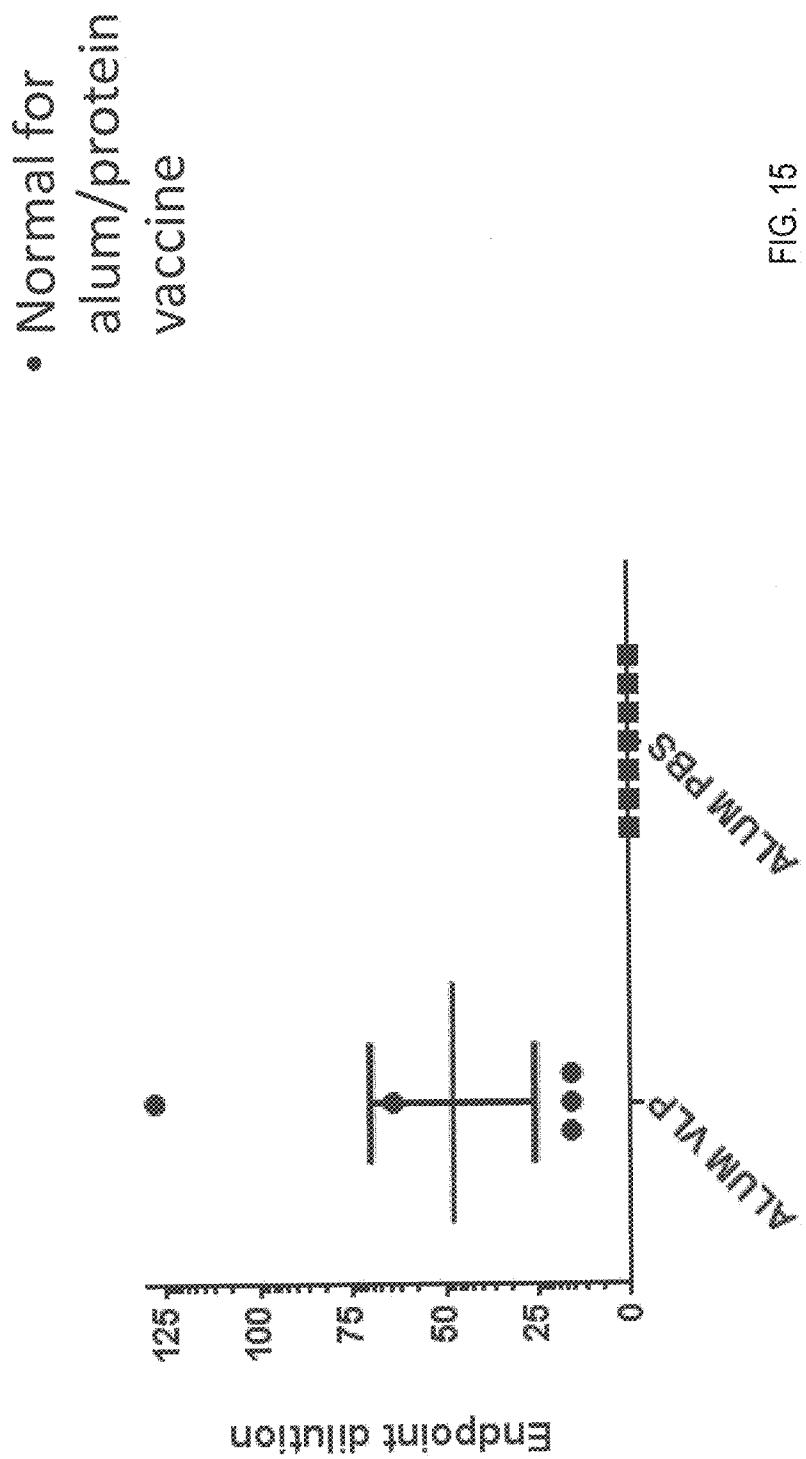


FIG. 15

Survival and morbidity

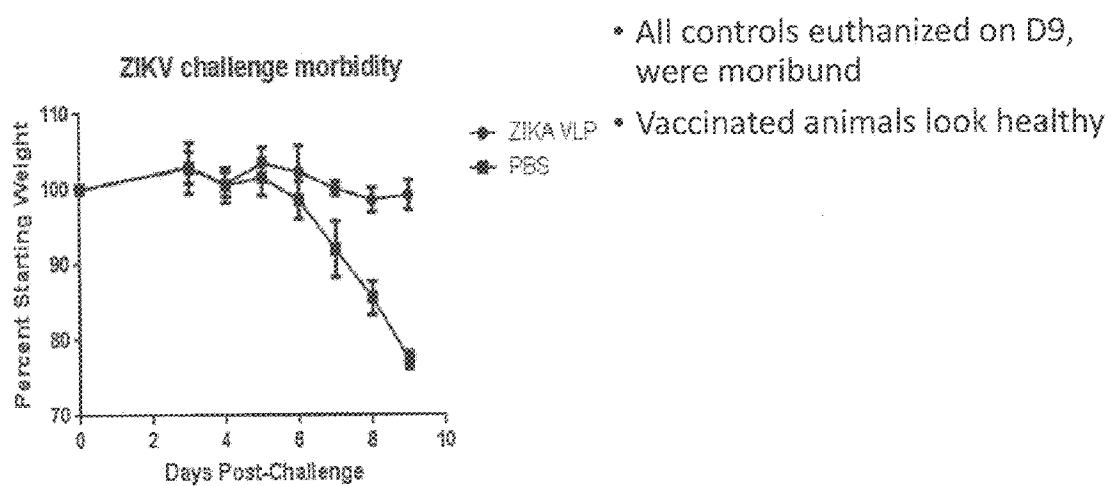


FIG. 16

FIG. 17A.

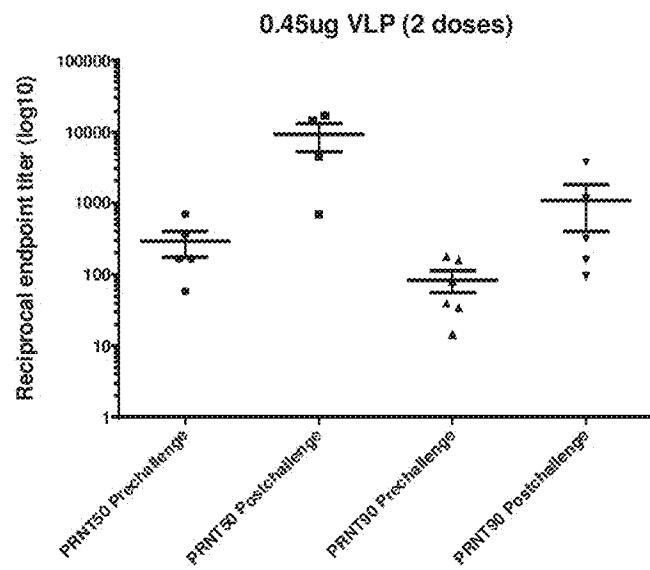


FIG. 17B.

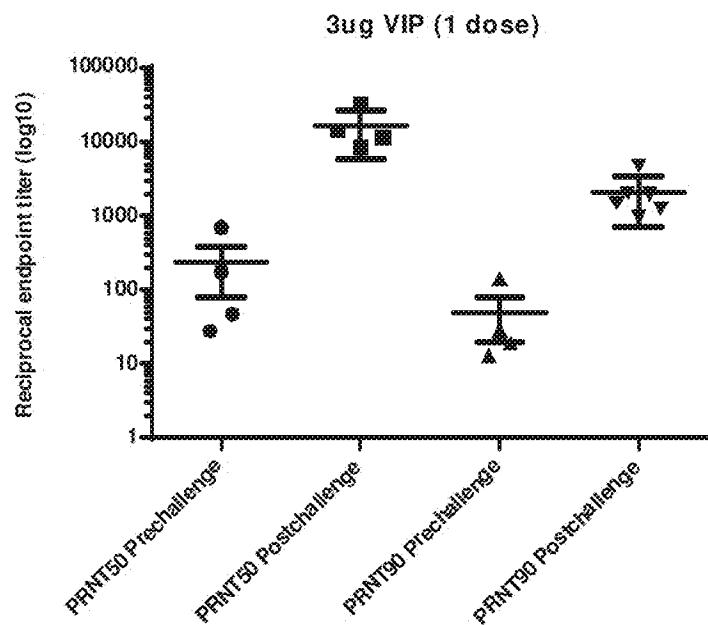


FIG. 17C

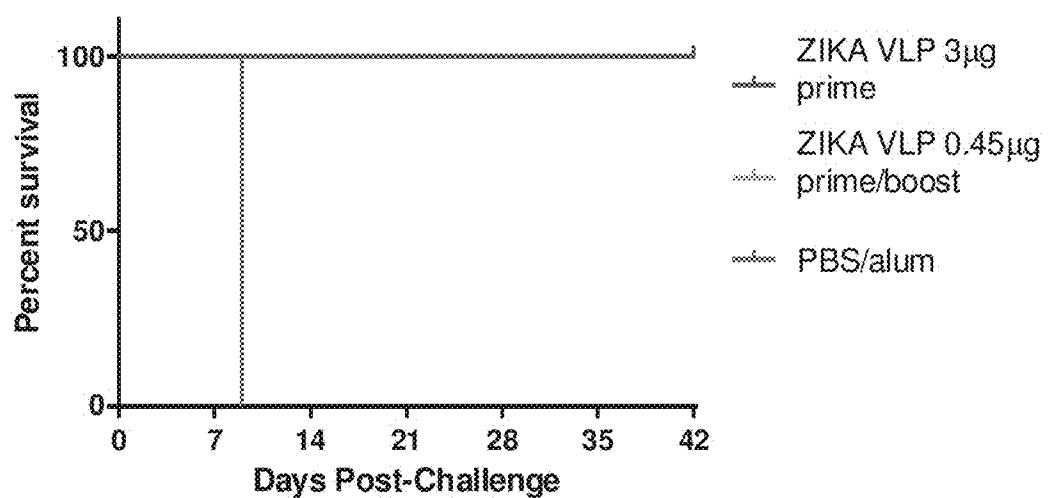


FIG. 18A.

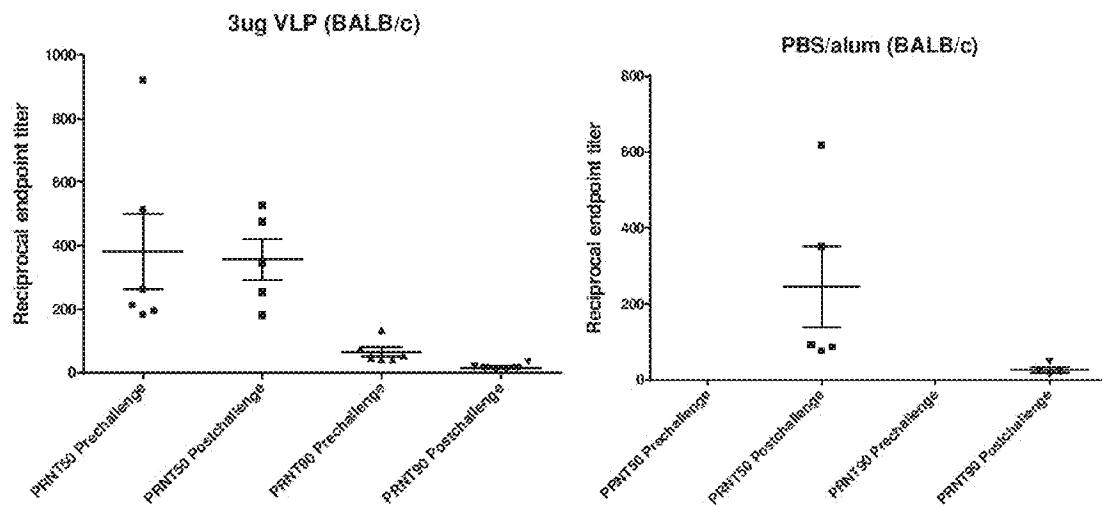


FIG. 18B.

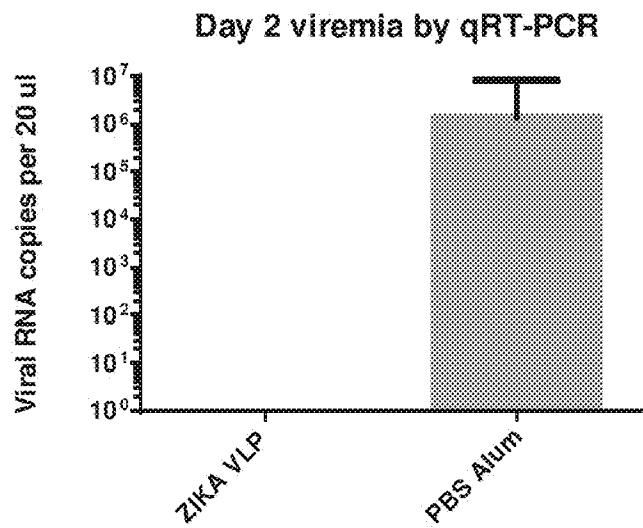
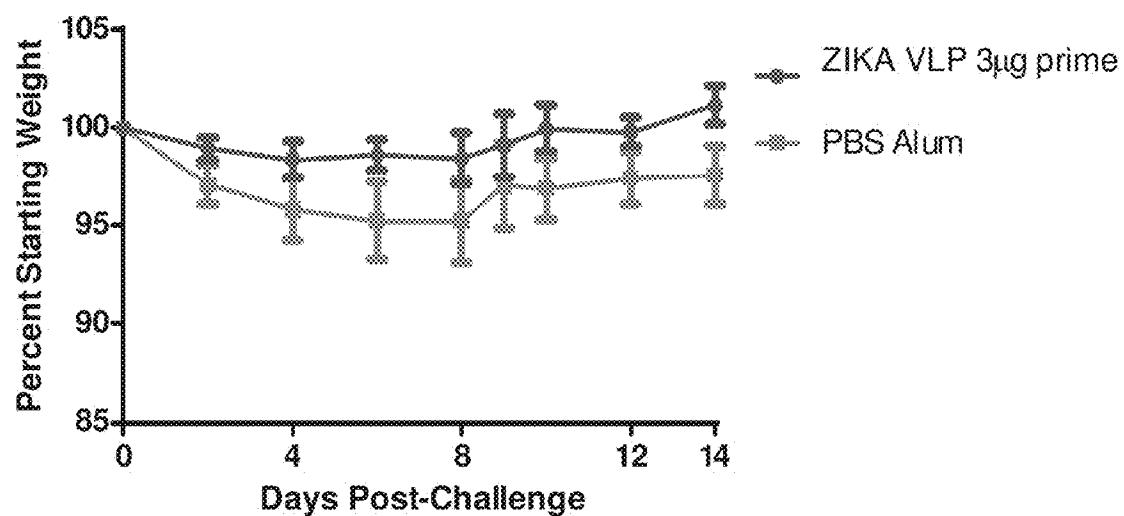


FIG. 18C.



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 incorporated 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-1 α 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 an intron, internal ribosome entry sequence, or an enhancer sequence, or any combination 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 encoding flavivirus 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 flavivirions 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 flavivirions 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. 1A-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) 3.5×10⁴ 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. 2A-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 TCID₅₀. F) PRNT₅₀ and PRNT₉₀ values (+/-SD) of serum samples taken from ZIKVLP vaccinated AG129 mice post challenge, and pre challenge serum from PBS/alum mice.

[0014] FIGS. 3A-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. 5A-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. 6A-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. 8A-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 TCID₅₀ 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. 17A-C. Dose response of ZIKVLPS in AG129 mice. A-B) PRNT₅₀ and PRNT₉₀ 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. 18A-C. Protection of ZIKVLPS in BALB/c mice. A) PRNT₅₀ and PRNT₉₀ 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 core 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 association 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 sub-unit 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 through 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 vaccinated 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 LD₅₀s). 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; tensioactive 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 algamulin, 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, poly-anhydrides, dextrans, as well as particles produced from natural materials like alginates, gelatine 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 salts, 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), liposomes, 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 galactomannans.

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 μ g, or 1 to 100 μ g, of VLPs. In one embodiment, the vaccine may contain about 100 μ g to about 500 μ g 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 μ g of VLPs. In one embodiment, the vaccine may contain less than about 750 μ g of VLPs. In one embodiment, the vaccine may contain less than about 250 μ g of VLPs. In one embodiment, the vaccine may contain less than about 100 μ g of VLPs. In one embodiment, the vaccine may contain less than about 40 μ g of VLPs. The vaccine forming the main constituent of the vaccine composition of the invention may comprise a combination of different flavivirus 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, thiosemicarbazones, 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 anti-sera 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 anti-sera 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% 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

[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 pCMV 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 Turbo blot® 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, Nanoprobe 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 determined 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 infec-

tion, 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:

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

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 PRNT₅₀ and PRNT₉₀ values (GraphPad Prism software).

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SEQ ID NO: 9:
mknppkksggg frivnmlkrq varvspfggg krlpaglllg hgpirmvlai laflrftaik
pslglrinrwg svgkkeamei ikkfkdkdlaa mlriinarke kkrrgadtsv givgllltta
maaeavtrrgs ayymyldrnd ageaisfppt lgmmkcyiqi mdlghmc当地 msyecpmilde
gvepdvdew cnttstwvvy gtchhkkgea rrsrravt1p shstrklqtr sqtwlesrey
tkhlirvenw ifrnpgfala aaaiawllgs stsqkviy1v milliapays ircigvsnrd
fvegmsggtw vdvvlehggc vtvmaqdkt vdielvttv snmaevrsyc yeasisdm
dsrceptqgea yldkqsd1tqy vckrt1vdrg wgnqcg1fgk gsvtcakfa cskkmtgksi
qpenleyrim lsvhgqsqhsq mivndtghet denrakveit pnspraeatl ggf1gslgldc
eprtgldfd lyyltmnnkh wlvhkewfh1 iplphagad tgtpwhnmke alvefkda
krqtvvvlgs qegavhtala galeaemdga kgrlssghlk crlkmkd1rl kgvsy1cta
aftftkipae tlhgtvtvev qyagtgdgpk vpaqmvadmq tltpvgrlit anpviteste
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fgsvggalns lgkgihqifg aafks1f1ggm swfsq1l1g 11mw1glntk ngsis1mcla
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kqawedgicg issvsrmeni m1wrsvegeln aileengvql t1vvvgsvknp mwrgpqrlpv
pvnelp1ghwk awgksy1fvra aktnnsfvvd gd1l1kecp1lk hrawns1lve dhgfgvfhts
vwlkvredys lecdpav1gt avkgkeavhs dlgywiesek ndt1w1lkr1h liemktcewp
ksht1wt1dgi eesdl1i1ipks lagplshhnt regyrtqmkg pwhseeleir feecpgtkvh
veetcgtrgp slrsttasgr vieewccrec tmppplsfrak dgcwygmeir pr1kepesnlv
rsmvtagstd hmdhf1sg1v1 villmvgegl kkr1mttk1ii stsmav1vam ilggf1msd1
aklailmgat faemntggdv ahlaliaafk vrpall1vsfi franwtpres m1lalascl1

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-continued

qtaisalegd lmvlingfal awlairamvv prtdnitlai laaltplarg tllvawragl
atcggfmls lkgkgsvkkn lpfvmalgt avrlvdpinv vglllptrsg krsppsevl
tavglicala ggfakadiem agpmaavgll ivsyvvsgks vdmyieragd itwekdaevt
gnsprldval desgdfslve ddgppmreii lkvvlmticg mmpiaipfaa gawyvyyktg
krsgalwdvp apkevkget tdgvyrvmtr rllgstqvvg vgmqegvfht mwhvtksal
rsgegrldpy wgdvkqdlvs ycgpwkldaa wdghsevql1 appgerarn iqtlpgifkt
kdgdigaval dypagtsgsp ildkcgrvig lyngvvikn gsyvsaitqg rreeetpvec
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gyistrvemg eaaaifmtat ppgtrdafpd snspimdt evperawssg fdwvtdhsrk
twwfvpsvrn gneiaacltk agkrviqlsr ktfteffqkt khqewdfvvt tdisemganf
kadrvidsrr clkpvildge rvilagpmhv thasaaqrrg rigrnpnkpg deylyggca
etededhahwl earmlldniy lqdglasly rpeadkvaai egefklrteq rktfvelmrk
gdlpvwlayq vasagitytd rrwcfdgtn ntimedsvp evwtrhgekr vlpkprwmdar
vcsdhaalks fkefaagkrg aafgvmealg tlpghmterf qeaidnlavl mraetasrpy
kaaaqaqp pet letimllgll gtvsllgiffv lmrnkgigkm gfgmvtlgas awlmwlseie
pariacvliv vflllvvlip epekqrspqd nqmaiimva vglglitan elgwlerkts
dlshlmgrre egatigfsmid idlrpasawa iyaalttfit pavqhavtts ynnyslmama
tqagvlfmgm kgmpfyawdf gpvlmigcy sqltpltiv aiillvahvm ylipglqaaa
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wgeaqalita atstlwegsp nkywnsstat slcniffrgsy lagasliytv trnaglvkrr
gggtgetlge kwkarlnqms alefysykks gitevcreea rralkdgvat gghavsrgsa
klrlvvergy lqpygkvidl gcgrggwsyy aatirkvqev kgytkggph eepmlvqsyg
wnivrlksrv dvhmaaepc dtllcdiges ssspeveear tlrvlsmvvd wlekrpgafc
ikvlcpyst mmetlerlqr rvggglvrvp lsrnsthemy wvsgaksnti ksvsttsqll
lgrmdgprrp vkyeedvnlg sgtravvsc eapnmkiign rierirseha etwffdenhp
yrtwayhgsy eaptqgsass lingvvrls kpwdvvtgvt giamtdtppg qqqrkfekv
dtrvpdpqeg trqvmsmvss wlwkelgkhk rprvctkeef inkvrsnaal gaifeekew
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garflefeal gflnedhwmg rensgggveg lglqrlgyvl eemsripgr myaddtagwd
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avsgddcvvk piddrfahal rflndmgkvr kdtqewkpst gwdnweevpf cshhfnklhl
kdgrsivvpc rhqdeligra rvspgagws1 retaclaksy aqmwqllyfh rrdlrlmana
icssvpvdwv ptgrttwsih gkgewmtted mlvvwnrvwi eendhmedkt pvtkwtdipy
lgkredlwgc slighrprtt waenikntvn mvrrriigdee 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. 1A), 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. 1B, 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. 1B, 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 flavivirus 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 flavivirus 103 like particles with a size that ranged from 30-60 nm (data not show), and a typical size of about 50 nm (FIG. 1C). High magnification images demonstrated surface structures characteristic of flaviral envelope proteins (FIGS. 1D, E).

Administration of ZIKVLPs is Immunogenic and Protects Highly ZIKV Susceptible $\alpha/\beta/\gamma$ 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 cal-

culated 90% plaque reduction (PRNT₉₀) titer of 1:34. The PRNT₉₀ 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 weight 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 PRNT₉₀ and PRNT₅₀ 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 ZIKV-VLP vaccine can protect female mice from contracting ZIKV during pregnancy using established models for such studies (Miner et al., 2016). ZIKV-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)

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(SEQ ID NO: 1)

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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: atcgctggagacgcacccatccacgtgttttgcacccatcataaagacacccggaccatccagccctccggccgggaa cggtgcatggaaacgcggattccccgtgccaagagtggactcaccgtccggatctcagcaaggag-

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gtaaaccctgcctccaaatgtgcctcatacgtcgtcaatctccgcgag-
gactggggaccctgtgacgac (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.

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[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):

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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):

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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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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 LD₅₀s) 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-γ) 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, Nanoprobe 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% Inject 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 intradermal (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 naïve 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 TCID₅₀ 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 (TCID₅₀s). 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 determined 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 virus 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 horseradish-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)-horseradish 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:

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

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 PRNT₅₀ and PRNT₉₀ 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. 1A), 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. 1B, 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. 1B, 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 flavivirus 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. 1C-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. 2A), 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. 2B). 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. 2B 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. 2D) and TCID₅₀ assay (ZIKVLP= 1.3×10^2 TCID₅₀s, PBS/alum 2.8×10^5 TCID₅₀s $p=0.0493$, FIG. 2E).

ZIKVLPs Elicit Plaque Reducing Neutralizing Antibody Titers in Mice That Can Be Passively Transferred to Naive 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 (PRNT₅₀) titer of 1:157. The PRNT₅₀ titer increased 2 weeks post challenge (GMT=5122) (FIG. 2F).

[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. 2F), 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. 3A-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. 3A-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 μ g ZIKVLPs adjuvanted with alum. An additional group of mice ($n=5$) was vaccinated with a prime and boost of 0.45 μ g 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. 17A). Eight weeks following primary vaccination mice were challenged with 200 PFU ($>1000 LD_{50}$ s) of ZIKV by the ID route. All mice administered a prime of 3 μ g or a prime and boost of 0.45 μ g ZIKVLPs survived throughout the 6 week challenge period (FIG. 17C) 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. 17A-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. 22A). Mice vaccinated with ZIKVLPs were completely protected from viremia on day 2 post challenge (FIG. 18B), and maintained weight throughout the challenge period (FIG. 18C). 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. 18A). Antibody titers in vaccinated mice decreased, but were not significantly different than before ZIKV challenge (FIG. 18A).

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 ($>400 \text{ LD}_{50}$ s) with no morbidity or mortality. Pre-challenge GMT neutralizing titers were 1:32, and pooled pre-challenge serum PRNT₉₀ and PRNT₅₀ 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 (Lazeer 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 $>1000 \text{ LD}_{50}$ s had low levels of viremia ($1.3 \times 10^2 \text{ TCID}_{50}$ s, FIG. 2E) 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 flavivirus 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 (PRNT₅₀ 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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<210> SEQ ID NO 4
<211> LENGTH: 392
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic oligonucleotide

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ccgtccggat ctcagcaagc aggtatgtac tctccagggttggccctgtat tccccagtc	180
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<210> SEQ ID NO 5
<211> LENGTH: 4251
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic oligonucleotide
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<400> SEQUENCE: 5

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cattnccccg aaaagtgc当地 cctgacgtcg ncggatcggg agatctccnn nnnnnnnnn
nnnnnnnnnn nnnnnnnnnn gctctgatgc cgcatagtttta agccagtttac tgctccctgc 180
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<210> SEQ ID NO 6

<211> LENGTH: 867

<212> TYPE: PRT

<213> ORGANISM: Zika virus

<400> SEQUENCE: 6

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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 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			
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Phe Ser Leu			
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 <210> SEQ ID NO 7			
<211> LENGTH: 3423			
<212> TYPE: PRT			
<213> ORGANISM: Zika virus			
 <400> SEQUENCE: 7			
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Leu Pro Ala Gly 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
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Thr	Thr	Thr	Val	Ser	Asn	Met	Ala	Glu	Val	Arg	Ser	Tyr	Cys	Tyr	Glu
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Ala	Ser	Ile	Ser	Asp	Met	Ala	Ser	Asp	Ser	Arg	Cys	Pro	Thr	Gln	Gly
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Glu	Ala	Tyr	Leu	Asp	Lys	Gln	Ser	Asp	Thr	Gln	Tyr	Val	Cys	Lys	Arg
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Thr	Leu	Val	Asp	Arg	Gly	Trp	Gly	Asn	Gly	Cys	Gly	Leu	Phe	Gly	Lys
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Gly	Ser	Leu	Val	Thr	Cys	Ala	Lys	Phe	Ala	Cys	Ser	Lys	Lys	Met	Thr
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Gly	Lys	Ser	Ile	Gln	Pro	Glu	Asn	Leu	Glu	Tyr	Arg	Ile	Met	Leu	Ser
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Val	His	Gly	Ser	Gln	His	Ser	Gly	Met	Ile	Val	Asn	Asp	Thr	Gly	His
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Glu	Thr	Asp	Glu	Asn	Arg	Ala	Lys	Val	Glu	Ile	Thr	Pro	Asn	Ser	Pro
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Arg	Ala	Glu	Ala	Thr	Leu	Gly	Gly	Phe	Gly	Ser	Leu	Gly	Leu	Asp	Cys
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Glu	Pro	Arg	Thr	Gly	Leu	Asp	Phe	Ser	Asp	Leu	Tyr	Tyr	Leu	Thr	Met
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Asn	Asn	Lys	His	Trp	Leu	Val	His	Lys	Glu	Trp	Phe	His	Asp	Ile	Pro
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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					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					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	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 Ser Thr Ser Met
 1170 1175 1180
 Ala Val Leu Val Ala Met Ile Leu 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 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 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 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 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
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
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
Lys 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
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
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 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 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 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										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										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	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										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										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										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
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
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
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 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 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
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
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
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
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 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 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 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 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 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 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 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 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 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 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 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
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
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
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
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
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
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Gly	Leu	Lys	Lys	Arg	Met	Thr	Thr	Lys	Ile	Ile	Ser	Thr	Ser	Met	
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Ala	Val	Leu	Val	Ala	Met	Ile	Leu	Gly	Gly	Phe	Ser	Met	Ser	Asp	Leu
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Ala	Lys	Leu	Ala	Ile	Leu	Met	Gly	Ala	Thr	Phe	Ala	Glu	Met	Asn	Thr
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Gly	Gly	Asp	Val	Ala	His	Leu	Ala	Ile	Ala	Ala	Phe	Lys	Val	Arg	
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Pro	Ala	Leu	Leu	Val	Ser	Phe	Ile	Phe	Arg	Ala	Asn	Trp	Thr	Pro	Arg
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Glu	Ser	Met	Leu	Leu	Ala	Leu	Ala	Ser	Cys	Leu	Leu	Gln	Thr	Ala	Ile
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Ser	Ala	Leu	Glu	Gly	Asp	Leu	Met	Val	Leu	Ile	Asn	Gly	Phe	Ala	Leu
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Ala	Trp	Leu	Ala	Ile	Arg	Ala	Met	Val	Val	Pro	Arg	Thr	Asp	Asn	Ile
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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
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Ser	Glu	Val	Leu	Thr	Ala	Val	Gly	Leu	Ile	Cys	Ala	Leu	Ala	Gly	Gly
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Phe	Ala	Lys	Ala	Asp	Ile	Glu	Met	Ala	Gly	Pro	Met	Ala	Ala	Val	Gly
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Leu	Leu	Ile	Val	Ser	Tyr	Val	Val	Ser	Gly	Lys	Ser	Val	Asp	Met	Tyr
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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
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Ser	Leu	Val	Glu	Asp	Asp	Gly	Pro	Pro	Met	Arg	Glu	Ile	Ile	Lys	
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Val	Val	Leu	Met	Thr	Ile	Cys	Gly	Met	Asn	Pro	Ile	Ala	Ile	Pro	Phe

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Ala Ala Gly Ala Trp Tyr Val Tyr Val Lys Thr Gly Lys Arg Ser Gly		
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Ala Leu Trp Asp Val Pro Ala Pro Lys Glu Val Lys Lys Gly Glu Thr		
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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
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
Phe Glu Pro Ser Met Leu 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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Glu Ala Ile Lys Thr Arg Leu Arg Thr Val Ile Leu Ala Pro Thr Arg		
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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
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		
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Asp Pro Ser Ser Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Glu		
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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
Glu Val Pro Glu Arg Ala Trp Ser Ser Gly Phe Asp Trp Val Thr Asp		
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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 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 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

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Arg	Glu	Glu	Gly	Ala	Thr	Ile	Gly	Phe	Ser	Met	Asp	Ile	Asp	Leu	Arg
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Cys	Tyr	Ser	Gln	Leu	Thr	Pro	Leu	Thr	Leu	Ile	Val	Ala	Ile	Ile	Leu
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Ala	Arg	Ala	Ala	Gln	Lys	Arg	Thr	Ala	Ala	Gly	Ile	Met	Lys	Asn	Pro
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Lys	Gly	Gly	Pro	Gly	His	Glu	Glu	Pro	Met	Leu	Val	Gln	Ser	Tyr	Gly
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Ala	Glu	Pro	Cys	Asp	Thr	Leu	Leu	Cys	Asp	Ile	Gly	Glu	Ser	Ser	Ser
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Gly	Asp	Trp	Leu	Glu	Lys	Arg	Pro	Gly	Ala	Phe	Cys	Ile	Lys	Val	Leu

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Cys Pro Tyr Thr Ser Thr Met Met Glu Thr Leu Glu Arg Leu Gln Arg		
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Arg Tyr 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
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
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		
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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
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
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

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 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
 3140 3145 3150

 Met Gln Asp Leu Trp Leu Leu Arg Arg Ser Glu Lys Val Thr Asn Trp
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 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 Val
 3380 3385 3390

 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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<210> SEQ ID NO 10
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Zika virus

<400> SEQUENCE: 10

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<210> SEQ ID NO 11
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<213> ORGANISM: Zika virus

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catggaccca	t c a g a t g g t	t t t g g c g a t a	c t a g c c t t c	t g a g a t t c a c	a g c a a t c a a g	180
ccatcaactgg	g c c t c a t c a a	t a g a t g g g g t	t c c g t g g g g a	a g a a g g a g g c	t a t g g a a a t a	240
ataaaaaaaagt	t c a a g a a a g a	t c t t g c t g c c	a t g t t g a g a a	t a a t c a a t g c	t a g g a a g g a g	300
aggaagagac	g t g g a g c t g a	t g c c a g c a t c	g g a a t c g t c a	g c c t c c t g c t	g a c t a c a g t c	360
atggcagcag	a g a t c a c t a g	a c g c g g a g t	g c a t a c t a c a	t g t a c t t g g a	c a g g a g c g a t	420
g c t g g t a a g g	c c a t t t c t t	c g t t a c c a c a	c t g g g g g t g a	a c a a a t g c c a	t g t g c a g a t c	480
atggacac	c g c a t a t g t g	t g a c g c c a c c	a t g a g t t a t g	a g t g c c c c a t	g c t g g a c g a g	540
g g a g t g g a g c	c a g a t g a c g t	c g a t t g c t g g	t g c a a c a c g a	c a t c a a c t t g	g g t t g t g t a c	600
g g a a c c t g t c	a t c a t a a a a a	a g g t g a a g c a	c g a c g a t c c a	g a a g a g c c g t	g a c g c t t c c t	660
t c t c a c t c a	c a a g g a a g t t	g c a a a c g c g a	t c g c a g a c t t	g g o t g a a t c	a a g a g a a t a c	720
a c a a a g c a c c	t g a t c a a g g t	t g a g a t t g g	a t a t t c a g g a	a c c c c g g g t	t g c g c t a g t g	780
g c t g t a g c t a	t t g c c t g g c t	c c t g g g a a g c	t c g a c g a g c c	a a a a a g t c a t	a t a c t t g g t c	840
a t g a t t t g t	t g a t t g c c c	g g c a t a c a g t	a t c a g g t g c a	t a g g a t t g a g	c a a t a g a g a c	900
t t c g t g g a g g	g c a t g t c a g g	t g g g a c t t g g	g t t g a t g t t g	t c t t g g a a c a	t g g a g g t t g t	960
g t c a c c g t g a	t g g c a c a g g a	c a a g c c a a c a	g t t g a c a t a g	a g t t g g t c a c	g a c a a c g g t t	1020
a g c a a c a t g g	c c g a g g t g a g	a t c c t a c t g c	t a c g a g g c a t	c a a t a t c g g a	c a t g g e t t c g	1080
g a c a g t c g c t	g c c c a a c a c a	a g g t g a a g c c	t a c c t t g a c a	a g c a g t c a g a	c a c t c a a t a t	1140
g t c t g t a a a a	g a a c a t t g g t	g g a c a g a g g t	t g g g a a a t g	g g t g t g g a c t	t t t t g g a a g	1200
g g g a g c t t g g	t g a c g t g t g c	c a a g t t a c a	t g c t c c a a g a	a a a t g a c a g g	g a a g a g c a t c	1260
c a g c c g g a g a	a c t t g g a g t a	c c g g a t a a t g	c t a t c a g t g c	a t g g a t c c c a	g c a c a g t t g g	1320
a t g a t t g t g a	a t g a c g a a a a	c a g a c a a a a	g t c g a g g t t a	c a c c c a a t t c	a c c a a g a g c a	1380
g a a g c a a c c t	t g g g a g g t t t	t g g a a g c c t g	g g a c t t g a t t	g t g a a c c a a g	g a c a g g c t t	1440
g a c t t t c a g	a t c t g t a t t a	c c t g a c c a t g	a a c a a t a a g c	a t t g g t t g g t	g c a c a a a g a g	1500
t g g t t c a t g	a c a t c c c a t t	a c c t t g g c a t	t c t g g t g c a g	a c a c t g a a a c	t c c a c a c t t g g	1560
a a c a a c a a a g	a g g c a c t g g t	g g a g g t t c a a g	g a c g c c c a c g	c c a a g a g g c a	a a c t g t t g t g	1620
g t t c t g g g g a	g c c a a g a a g g	a g c c g t t c a c	a c g g c t c t g	c t g g a g g t c t	g g a g g c t g a g	1680
a t g g a t g g t g	c g a a g g g a a g	g c t a t c c t c a	g g c c a t t t g a	a a t g c c g c t	a a a a a t g g a c	1740
a a g c t t a g g t	t g a a g g g t g t	t g c a t a t t c c	c t g t g t a c c g	c a g c g t t c a c	a t t c a c c a a g	1800
g t t c c a g c t g	a a c a t t g c a	t g g a a c a g t c	a c a g t g g a g g	t g c a g t a t g c	a g g g a g g g a t	1860
g g a c c c t g c a	a g g t c c o a g c	c c a g a t g g c g	g t g g a c a t g c	a g a c c c t g a c	c c a g a t t g g a	1920
aggcgtataa	c g g c t a a c c c	t g t g a t c a c t	g a a g c a c t g	a g a a t t c a a a	g a t g a t t g g	1980
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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

tadecylammonium, 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.

15. The method of claim **14** wherein the mammal is a female mammal.

16. The method of claim **14** wherein the mammal is a human.

17. The method of claim **14** wherein the flavivirus is a Zika virus.

18. 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.

19. The method of claim **14** wherein the composition comprising the flavivirus like particle is administered intramuscularly, subcutaneously or intranasally.

20. The method of claim **14** wherein the composition inhibits flavivirus infection.

21. The method of claim **14** wherein the composition treats flavivirus infection.

* * * * *