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(54) **CHIMERIC WEST NILE/ZIKA VIRUSES AND METHODS OF USE**

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(51) **Int. Cl.**

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A61K 39/00	(2006.01)
C07K 14/005	(2006.01)
C12N 7/00	(2006.01)
A61K 39/295	(2006.01)
G01N 33/533	(2006.01)

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

CPC ***A61K 39/12*** (2013.01); ***C07K 14/005*** (2013.01); ***C12N 7/00*** (2013.01); ***G01N 33/533*** (2013.01); *A61K 2039/525* (2013.01); *A61K 2039/5252* (2013.01); *A61K 2039/5254* (2013.01); *A61K 2039/53* (2013.01); *C12N 2770/24122* (2013.01); *C12N 2770/24134* (2013.01); *C12N 2770/24141* (2013.01); *C12N 2770/24144* (2013.01); *Y02A 50/392* (2018.01); *Y02A 50/394* (2018.01)

(58) **Field of Classification Search**

CPC C12N 7/00; C12N 2770/24122; C07K 14/005; Y02A 50/386; Y02A 50/388

See application file for complete search history.

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WO	WO2015196094	* 12/2015

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(57) **ABSTRACT**

Chimeric flaviviruses that include non-coding regions, non-structural proteins, a capsid (C) protein and a portion of a premembrane (prM) signal sequence from West Nile virus (WNV), and a portion of a prM signal sequence, a prM protein and an E protein from Zika virus (VIKV) are described. Also described are compositions and methods for eliciting an immune response in a subject, such as an immune response directed against ZIKV. Diagnostic assays that utilize chimeric West Nile/Zika viruses are further described.

39 Claims, 6 Drawing Sheets

Specification includes a Sequence Listing.

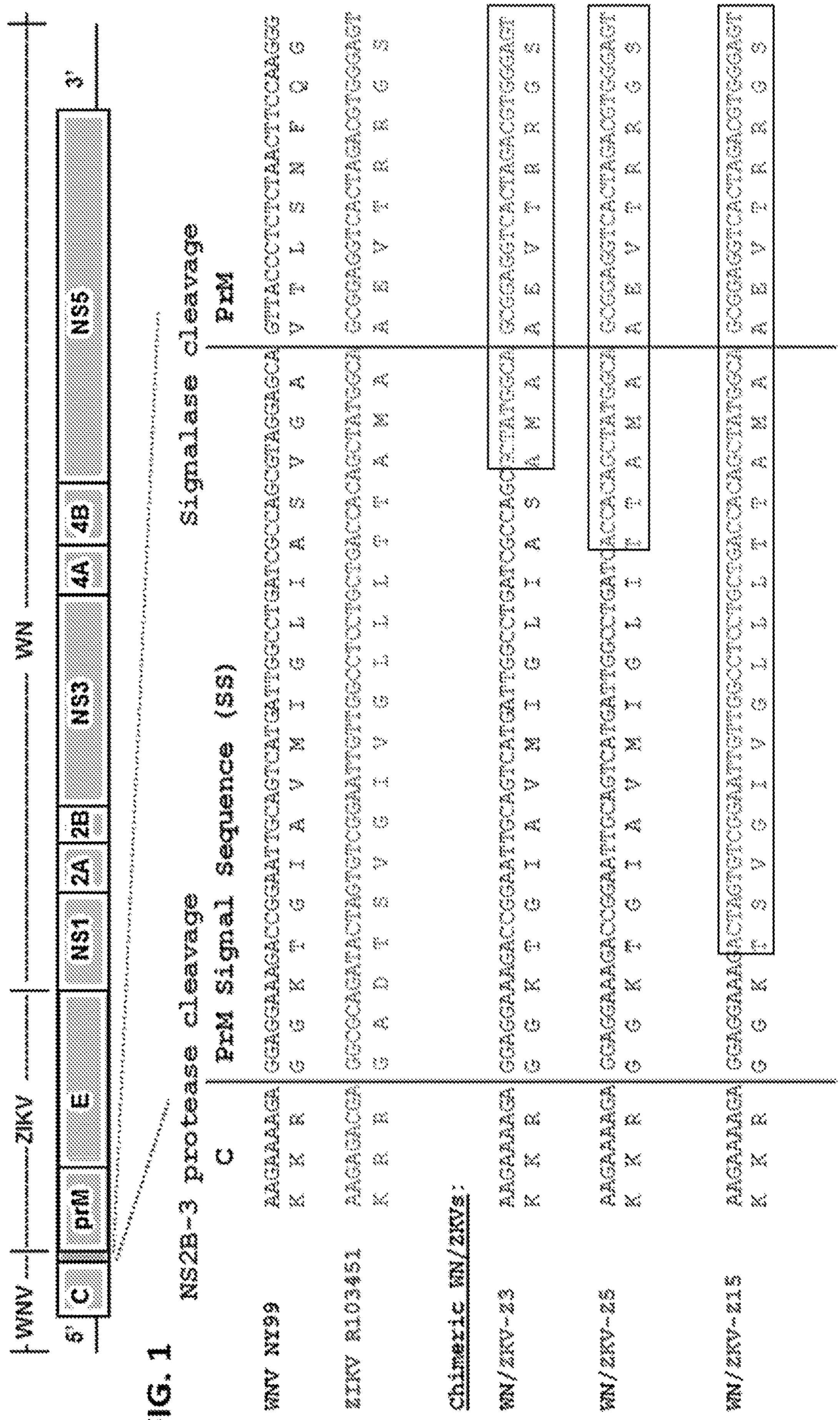
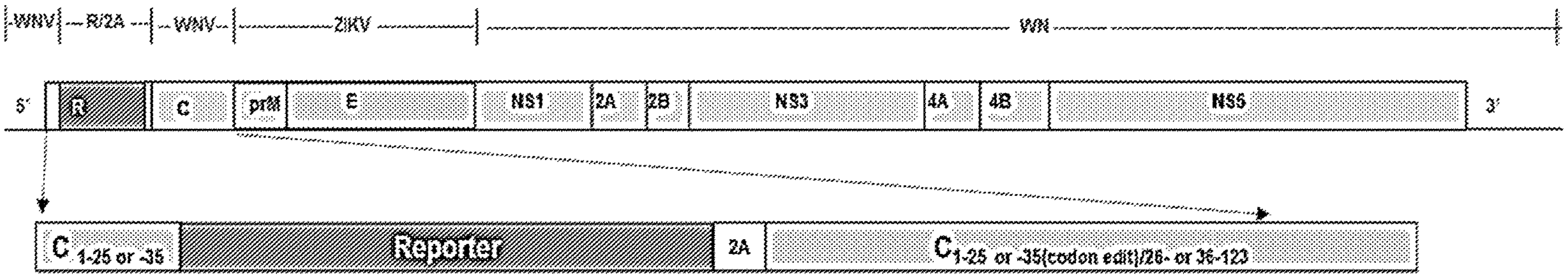

WNV
ZIKV
WN
5'
3'
C
prM
E
NS1
2A
2B
NS3
4A
4B
NS5
NS2B-3 protease cleavage
Signalase cleavage
C
PrM Signal Sequence (SS)
PrM
WNV NY99
ZIKV R103451
Chimeric WN/ZKVs:
WN/ZKV-Z3
WN/ZKV-Z5
WN/ZKV-Z15

FIG. 1

Type I reporter constructs:

- First C gene box [C1-25 or -35]: contains 1-25 or 1-35 amino acids of C protein: non-codon edited
- Reporter Gene can be ZsGreen, mWasabi, or Luciferase.
- 2A self cleavage peptide could be F2A or P2A
- Second C gene box [C1-25 or 1-35(edited codons)/26- or 36-123 contains entire C gene of WNV, the first 25 or 35 amino acids were codon edited (silent mutations), and rest codons are as wild-type codons of WNV C

FIG. 2



Type II reporter constructs:

- Reporter Gene can be ZsGreen, mWasabi, or Luciferase.
- 2A self cleavage peptide could be F2A or P2A
- The reporter cassette is located after the first 3 AA of the WNV signal sequence encoding "GGK".
- The sequence encoding the entire 18 AA of the ZIKV signal sequence (red fonts) are included between 2A and prM genes

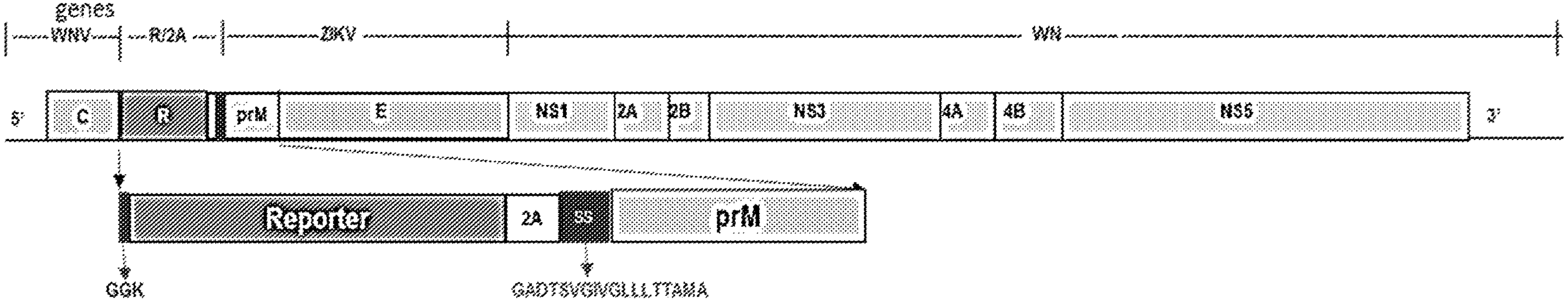


FIG. 3

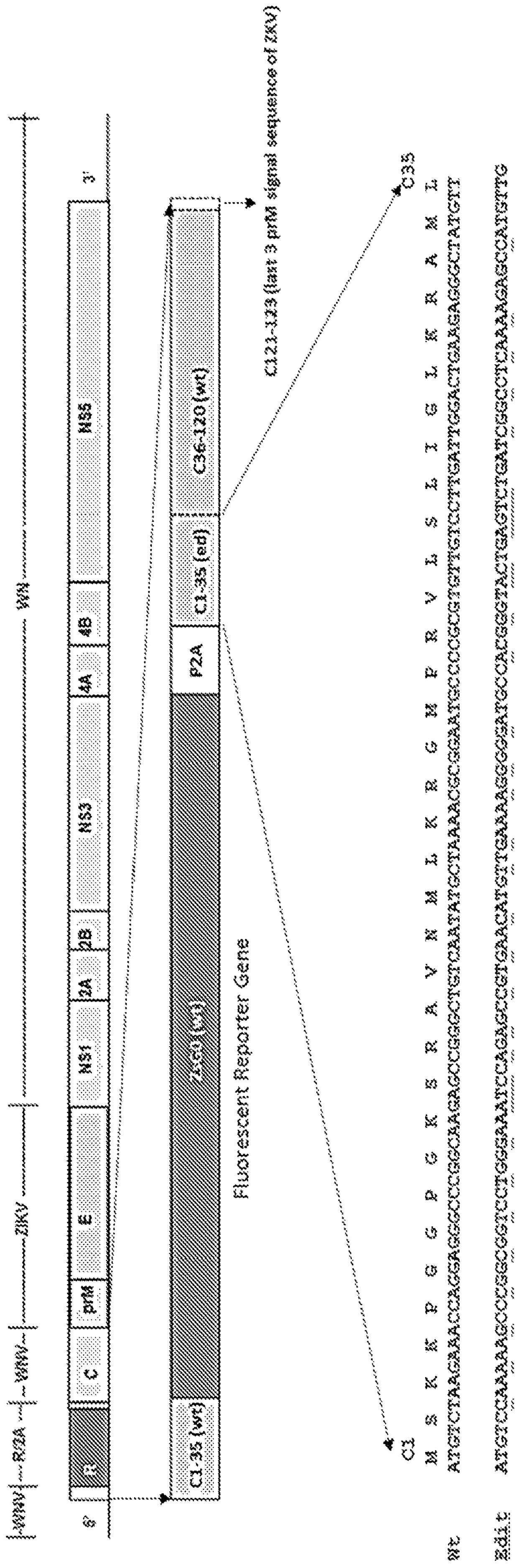

WNV
R/2A
WNV
ZIKV
WN
5'
3'
R
C
prM
E
NS1
2A
2B
NS3
4A
4B
NS5
C1-35 (wt)
ZsG (wt)
P2A
C1-35 (ed)
C36-120 (wt)
C121-123 (last 3 prM signal sequence of ZIKV)
Fluorescent Reporter Gene
C1
C35
Wt
Edit

FIG. 4

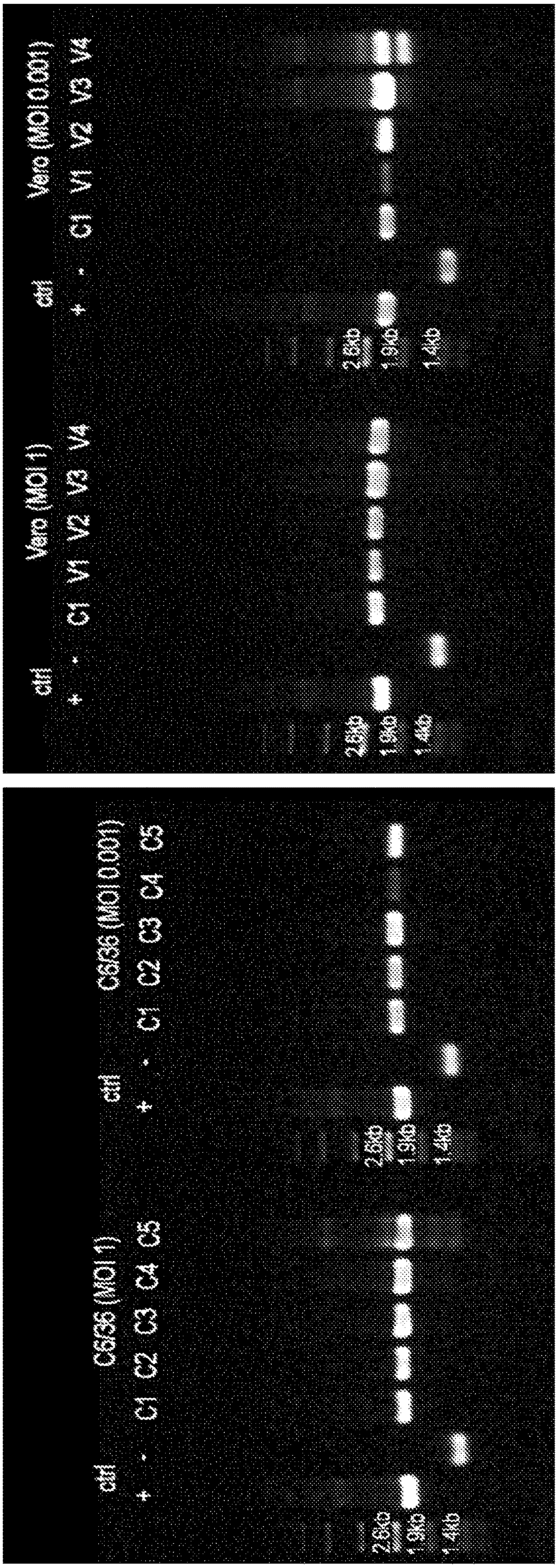

Vero (MOI 0.001)
ctrl
+ - C1 V1 V2 V3 V4
2.6kb
1.9kb
1.4kb
Vero (MOI 1)
ctrl
+ - C1 V1 V2 V3 V4
2.6kb
1.9kb
1.4kb
C6/36 (MOI 0.001)
ctrl
+ - C1 C2 C3 C4 C5
2.6kb
1.9kb
1.4kb
C6/36 (MOI 1)
ctrl
+ - C1 C2 C3 C4 C5
2.6kb
1.9kb
1.4kb

FIG. 5

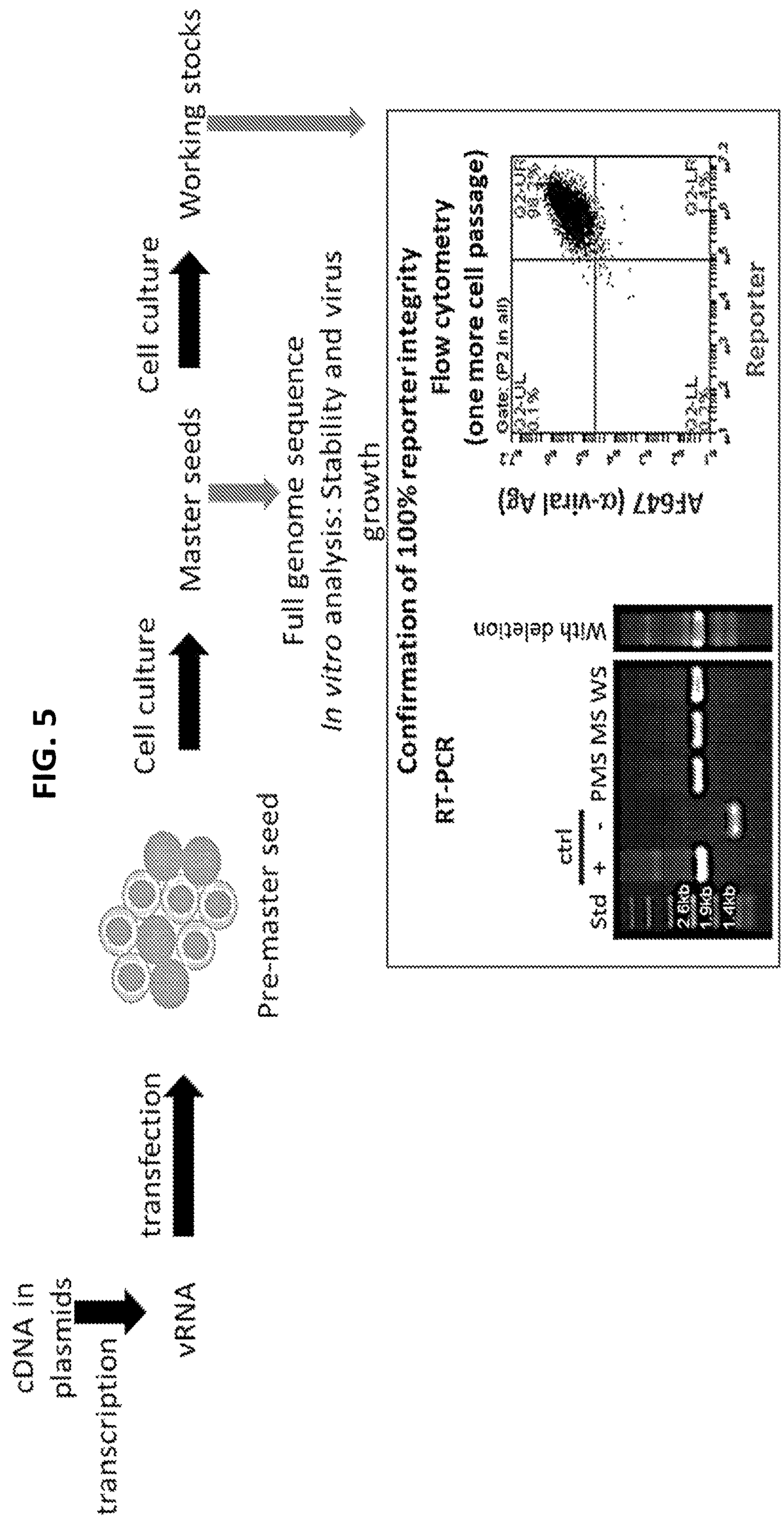

cDNA in plasmids
transcription
vRNA
transfection
Pre-master seed
Cell culture
Master seeds
Cell culture
Working stocks
Full genome sequence
In vitro analysis: Stability and virus growth
Confirmation of 100% reporter integrity
RT-PCR
ctrl
Std + - PMS MS WS
With deletion
2.6kb
1.9kb
1.4kb
Flow cytometry
(one more cell passage)
AF647 (α-viral Ag)
Reporter

FIG. 6

Comparison of Neutralization Assays

	PRNT	Immuno-mFRNT	Fluoro-mFRNT
Detection	Plaque	Immunospot	Fluorospot
Processing	1-2 overlays Plaque staining Plaque visualization	1 overlay Fixation and Immunostaining Foci image	none Live cell image (w/o fixation)
Plate Format	6-, 12-, 24-well	96-, 384-well	96-, 384-well
Labor-intensive	High	High	Low
Estimated minimal time*	WN/ZKV: 72 hours (wt ZKV: 120 hours)	WN/ZKV: 28 hours (wt ZKV: 28/40 hours**)	R-WN/ZKV: 25 hours
Summary	Slow and labor-intensive	Fast and automatic readout, but labor-intensive	Fast and automatic readout, minimum procedures (high-throughput)

* Minimal duration starts from cell infection with virus-Ab complex and ends at result readout
** 40 hours is better than 28 hours

CHIMERIC WEST NILE/ZIKA VIRUSES AND METHODS OF USE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is the U.S. National Stage of International Application No. PCT/US2017/040818, file Jul. 6, 2017, published in English under PCT Article 21(2), which claims the benefit of U.S. Provisional Application No. 62/359,807, filed Jul. 8, 2016, which is herein incorporated by reference in its entirety.

FIELD

This disclosure concerns chimeric flaviviruses, particularly chimeric West Nile virus/Zika virus constructs. Further, it relates to methods of using the chimeric viruses for therapeutic and diagnostic applications.

BACKGROUND

Zika virus, a flavivirus classified within the Flaviviridae with other important mosquito-borne viruses, including yellow fever, dengue, West Nile and Japanese encephalitis viruses, has spread rapidly in a hemispheric-wide epidemic since the virus was introduced to Brazil in 2015, reaching Central and North Americas, including territories of the United States and now threatening the continental U.S. Initially isolated in 1947 in Uganda, the virus was first linked to human disease in 1952 and has been recognized sporadically as a cause of mild, self-limited febrile illness in Africa and Southeast Asia (Weaver et al., *Antiviral Res* 130:69-80, 2016; Faria et al., *Science* 352(6283):345-349, 2016). However, in 2007, an outbreak appeared in the North Pacific island of Yap, transferred there presumably from Asia, and subsequently disseminated from island to island across the Pacific, leading to an extensive outbreak in 2013-2014 in French Polynesia, with subsequent spread to New Caledonia, the Cook Islands, and ultimately to Easter Island, far to the East. An Asian lineage virus subsequently was transferred to the Western Hemisphere by routes that remain undetermined (Faria et al., *Science* 352(6283):345-349, 2016). The virus is transmitted anthropontically by *Aedes aegypti, A. albopictus* and possibly *A. hensilli* and *A. polynieseinsis* (Weaver et al., *Antiviral Res* 130:69-80, 2016).

In late 2015, a significant increase in fetal abnormalities (e.g. microcephaly) and Guillain-Barré syndrome (GBS) in areas of widespread Zika virus infection raised concerns that Zika virus might be much more virulent than originally thought and prompted the World Health Organization (WHO) to declare a Public Health Emergency of International Concern (PHEIC) (Heymann et al., *Lancet* 387 (10020):719-721, 2016).

SUMMARY

Disclosed herein are chimeric flaviviruses that include non-coding regions, a capsid (C) protein, a portion of a premembrane (prM) signal sequence, and non-structural proteins from West Nile virus (WNV); and a portion of a prM signal sequence, a prM protein and an envelope (E) protein from Zika virus (ZIKV). Also disclosed are compositions and methods for eliciting an immune response directed against ZIKV in a subject. Diagnostic assays that utilize the disclosed chimeric West Nile/Zika viruses are further described.

Provided herein is a nucleic acid chimera that includes nucleic acid sequence from a WNV and nucleic acid sequence from a ZIKV. In some embodiments, the nucleic acid chimera includes a first nucleic acid molecule comprising a 5' non-coding region, a nucleic acid encoding a C protein and non-structural proteins, and a 3' non-coding region, each from a WNV genome, wherein the C protein comprises a portion of a prM signal sequence from the WNV genome and a portion of a prM signal sequence from a ZIKV genome; and a second nucleic acid molecule operably linked to the first nucleic acid molecule, encoding a prM protein and an E protein from the ZIKV genome. In some examples, the portion of the prM signal sequence from the WNV genome includes the first 15 amino acids of the WNV prM signal sequence and the portion of the prM signal sequence from the ZIKV genome includes the last three amino acids of the ZIKV prM signal sequence. In other examples, the portion of the prM signal sequence from the WNV genome includes the first 13 amino acids of the WNV prM signal sequence and the portion of the prM signal sequence from the ZIKV genome includes the last five amino acids of the ZIKV prM signal sequence. In yet other examples, the portion of the prM signal sequence from the WNV genome includes the first three amino acids of the WNV prM signal sequence and the portion of the prM signal sequence from the ZIKV genome includes the last 15 amino acids of the ZIKV prM signal sequence.

Also provided herein is an immunogenic composition that includes an inactivated virus comprising a nucleic acid chimera disclosed herein, and a pharmaceutically acceptable carrier. Further provided is a method of eliciting an immune response against ZIKV in a subject by administering the immunogenic composition.

A method that includes inactivating a virus comprising a nucleic chimera disclosed herein is further provided by the present disclosure. The virus can be inactivated using any means known in the art, such as, but not limited to treating the virus with a chemical inactivation agent, high pressure, ultraviolet irradiation, gamma irradiation, or any combination thereof.

Further provided herein is a nucleic acid chimera that includes a first nucleic acid molecule comprising a 5' non-coding region, a nucleic acid encoding a C protein and non-structural proteins, and a 3' non-coding region, each from a WNV genome, wherein the C protein comprises a portion of a prM signal sequence from the WNV genome and a portion of a prM signal sequence from a ZIKV genome; and a second nucleic acid molecule operably linked to the first nucleic acid molecule, encoding a prM protein and an E protein from the ZIKV genome, and further includes a reporter gene, such as a reporter gene encoding a light-emitting protein, such as a fluorescent or bioluminescent protein.

Further provided herein are chimeric viruses that include a nucleic acid chimera disclosed herein.

Methods of detecting ZIKV-specific antibodies in a sample are also provided herein. In some embodiments, the method includes contacting the sample with a chimeric virus disclosed herein under conditions sufficient to form virus-antibody complexes if ZIKV antibodies are present in the sample; and detecting the virus-antibody complexes, thereby detecting ZIKV-specific antibodies in the sample.

In some embodiments, the method includes contacting the sample with a chimeric virus disclosed herein to form a virus-sample mixture, wherein virus-antibody complexes are formed in the virus-sample mixture if ZIKV-specific antibodies are present in the sample; inoculating a cell culture with the virus-sample mixture under conditions sufficient to allow plaque formation or micro-focus formation in the cell culture; and detecting a decrease in plaque formation or micro-focus formation in the cell culture as compared to a control cell culture, such as a control cell culture infected with virus only.

In some embodiments, the method includes providing a chimeric virus disclosed herein bound to a solid support; contacting the chimeric virus-bound solid support with the sample under conditions sufficient to form virus-antibody complexes if ZIKV-specific antibodies are present in the sample; contacting the virus-antibody complexes with a secondary antibody; and detecting binding of the secondary antibody to the virus-antibody complexes.

In some embodiments, the method includes providing a secondary antibody bound to a solid support; contacting the secondary antibody-bound solid support with the sample under conditions sufficient to allow binding of the secondary antibody to any ZIKV-specific antibodies present in the sample, thereby forming antibody-antibody complexes; contacting the antibody-antibody complexes with a chimeric virus disclosed herein under conditions sufficient for the chimeric virus to bind the ZIKV-specific antibodies, thereby forming immune complexes; and detecting the presence of the immune complexes.

In some embodiments, the method includes providing a ZIKV-specific antibody bound to a solid support; contacting the antibody-bound solid support with a chimeric virus disclosed herein under conditions sufficient for the chimeric virus to bind the ZIKV-specific antibody to form antibody-virus complexes; contacting the antibody-virus complexes with the sample to allow binding of any ZIKV-specific antibodies present in the sample to the chimeric virus, thereby forming immune complexes; contacting the immune complexes with a secondary antibody; and detecting binding of the secondary antibody to the immune complexes, thereby detecting ZIKV-specific antibodies present in the sample.

The foregoing and other objects, features, and advantages of the invention will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the genomic structure of chimeric West Nile/Zika viruses. Chimeric viruses contain prM-E of ZIKV in the genomic backbone of WNV. The chimeric C/prM junction site is enlarged to show the 3 different junction strategies. The NS2B-3 protease cleavage and signalase cleavage sites are indicated. WNV (NY99) and ZIKV (R103451; also referred to as "103451" in the GenBank database) nucleotide and amino acid sequences are shown. For the three chimeric viruses, boxes indicate the ZIKV portion of the sequence. The sequences shown include WNV NY99 (nucleotides 403-489 of SEQ ID NO: 17; amino acids 103-131 of SEQ ID NO: 18), ZIKV R103451 (nucleotides 411-497 of SEQ ID NO: 13 and amino acids 102-130 of SEQ ID NO: 14), WN/ZKV-Z3 (nucleotides 403-489 of SEQ ID NO: 3; amino acids 103-131 of SEQ ID NO: 4), WN/ZKV-Z5 (nucleotides 403-489 of SEQ ID NO: 5; amino acids 103-131 of SEQ ID NO: 6) and WN/ZKV-Z15 (nucleotides 403-489 of SEQ ID NO: 7; amino acids 103-131 of SEQ ID NO: 8).

FIG. **2** shows the genomic structure of chimeric West Nile/Zika reporter viruses. Two construct strategies (Type I and Type II) are shown in the figure. For Type I reporter constructs, the reporter cassette (including the reporter gene and a 2A peptide encoding sequence) is inserted 5' of the complete C gene, and a partial C gene encoding the first 25 or 35 amino acids is added 5' of the reporter cassette. The partial C gene provides a critical cyclization sequence connected to the 5' non-coding region for competent virus replication. The first 25 or 35 amino acids in the complete C gene is codon edited with silent mutations to minimize homologous recombination potential with the partial C gene. The reporter viruses WN/ZKV-ZsG0 (SEQ ID NOs: 9 and 10) and WN/ZKV-ZsG1 (SEQ ID NOs: 11 and 12) are examples of Type 1 constructs with ZsGreen and P2A as the reporter cassette for both. For Type II reporter constructs, the reporter cassette is inserted in the signal sequence region at the 3' end of the C gene. The first three amino acids (GGK) of the WNV signal sequence are retained in front of the reporter for correct NS2B-NS3 cleavage, and the entire 18 amino acids of the ZIKV signal sequence (residues 105-122 of SEQ ID NO: 14) are included between the 2A peptide and Zika virus prM for proper prM protein processing.

FIG. **3** is a schematic of the R-WN/ZKV-PR chimeric reporter virus. R-WN/ZKV-PR (also referred to as R-WN/ZKV) is a Type I reporter construct with ZsG0/P2A inserted after C1-35 of WNV and includes a complete WNV C gene downstream of P2A. In order to minimize homologous recombination between the partial C gene (C1-35(wt)) proceeding the reporter insert and the complete C gene following the reporter insert, the first 35 amino acids of the downstream C protein (C1-35(ed)) was edited to substitute specific nucleotides (indicated by underline) while maintaining the amino acid sequence.

FIG. **4** shows the genetic stability of ZsG0 in R-WN/ZKV-PR virus. R-WN/ZKV-PR was serially passaged in C6/36 cells (left) or Vero cells (right) at an MOI of 1 or an MOI of 0.001. ZsG0 gene was analyzed by RT-PCR with a primer set for amplifying a 2.27 kb cDNA fragment (nucleotides 1-2272 of R-WN/ZKV-PR), including the full ZsG0 and P2A. The reporter gene was intact after 5 passages in C6/36 cells at an MOI of 0.001, but showed deletion in a portion of the stock at an MOI of 1. In Vero cells, the reporter gene was stable up to 4 passages at an MOI of 1, but a significant portion of the 0.001 MOI passage-4 stock showed partial gene deletion.

FIG. **5** includes a schematic of the production of R-WN/ZKV reporter virus seed lots. Also shown are RT-PCR and flow cytometry analysis of the integrity of the R-WN/ZKV reporter virus.

FIG. **6** is a table showing a comparison of PRNT, immuno-mFRNT and fluoro-mFRNT assays when using WN/ZKV, R-WN/ZKV or wild-type Zika virus.

SEQUENCE LISTING

The nucleic and amino acid sequences listed in the accompanying sequence listing are shown using standard letter abbreviations for nucleotide bases, and three letter code for amino acids, as defined in 37 C.F.R. 1.822. Only one strand of each nucleic acid sequence is shown, but the complementary strand is understood as included by any reference to the displayed strand. The Sequence Listing is submitted as an ASCII text file, created on Jan. 2, 2019 448 KB, which is incorporated by reference herein. In the accompanying sequence listing:

SEQ ID NOs: 1 and 2 are WN/ZKV-3PR nucleotide and amino acid sequences, respectively.

SEQ ID NOs: 3 and 4 are WN/ZKV-3SPH nucleotide and amino acid sequences, respectively.

SEQ ID NOs: 5 and 6 are WN/ZKV-5SPH nucleotide and amino acid sequences, respectively.

SEQ ID NOs: 7 and 8 are WN/ZKV-15SPH nucleotide and amino acid sequences, respectively.

SEQ ID NOs: 9 and 10 are WN/ZKV-ZsG0 reporter nucleotide and amino acid sequences, respectively.

SEQ ID NOs: 11 and 12 are WN/ZKV-ZsG1 reporter nucleotide and amino acid sequences, respectively.

SEQ ID NOs: 13 and 14 are the nucleotide and amino acid sequences of Zika virus strain R103451.

SEQ ID NOs: 15 and 16 are the nucleotide and amino acid sequences of Zika virus strain PRVABC59.

SEQ ID NOs: 17 and 18 are the nucleotide and amino acid sequences of West Nile virus strain NY99, deposited under Genbank Accession No. AF196835.

SEQ ID NOs: 19 and 20 are R-WN/ZKV-PR reporter nucleotide and amino acid sequences, respectively.

DETAILED DESCRIPTION

I. Abbreviations

AST average survival time

C capsid protein

C(ss) prM signal sequence portion of C protein

CPE cytopathic effect

E envelope glycoprotein

ELISA enzyme-linked immunosorbent assay

GBS Guillain-Barré syndrome

mAb monoclonal antibody

mFRNT microfocus reduction neutralization test

NCR non-coding region

NS non-structural

Nt Abs neutralization antibodies

pfu plaque forming unit

p.i. post-infection

prM premembrane protein

PHEIC Public Health Emergency of International Concern

PRNT plaque reduction neutralization test

WHO World Health Organization

WNV West Nile virus

WN/ZKV West Nile/Zika virus chimera

ZIKV Zika virus

II. Terms and Methods

Unless otherwise noted, technical terms are used according to conventional usage. Definitions of common terms in molecular biology may be found in *Lewin's Genes X*, ed. Krebs et al, Jones and Bartlett Publishers, 2009 (ISBN 0763766321); Kendrew et al. (eds.), *The Encyclopedia of Molecular Biology*, published by Blackwell Publishers, 1994 (ISBN 0632021829); Robert A. Meyers (ed.), *Molecular Biology and Biotechnology: a Comprehensive Desk Reference*, published by Wiley, John & Sons, Inc., 1995 (ISBN 0471186341); and George P. Rédei, *Encyclopedic Dictionary of Genetics, Genomics, Proteomics and Informatics,* 3rd Edition, Springer, 2008 (ISBN: 1402067534).

Unless otherwise explained, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. It is further to be understood that all base sizes (lengths) or amino acid sizes (lengths), and all molecular weight or molecular mass values, given for nucleic acids or polypeptides are approximate, and are provided for description. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety for all purposes. All GenBank Accession Nos. mentioned herein are incorporated by reference in their entirety. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. In case of conflict, the present specification, including explanations of terms, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

In order to facilitate review of the various embodiments of the invention, the following explanations of specific terms are provided:

Adjuvant: A substance or vehicle that non-specifically enhances the immune response to an antigen. Adjuvants can include a suspension of minerals (alum, aluminum hydroxide, or phosphate) on which antigen is adsorbed; or water-in-oil emulsion in which antigen solution is emulsified in mineral oil (for example, Freund's incomplete adjuvant), sometimes with the inclusion of killed mycobacteria (Freund's complete adjuvant) to further enhance antigenicity. Immunostimulatory oligonucleotides (such as those including a CpG motif) can also be used as adjuvants (for example, see U.S. Pat. Nos. 6,194,388; 6,207,646; 6,214,806; 6,218,371; 6,239,116; 6,339,068; 6,406,705; and 6,429,199). Adjuvants also include biological molecules, such as costimulatory molecules. Exemplary biological adjuvants include IL-2, RANTES, GM-CSF, TNF-α, IFN-γ, G-CSF, LFA-3, CD72, B7-1, B7-2, OX-40L and 41 BBL.

Administer: As used herein, administering a composition (e.g. an immunogenic composition, such as a chimeric virus) to a subject means to give, apply or bring the composition into contact with the subject. Administration can be accomplished by any of a number of routes, such as, for example, topical, oral, subcutaneous, intramuscular, intraperitoneal, intravenous, intrathecal and intramuscular.

Antibody: A protein (or protein complex) that includes one or more polypeptides substantially encoded by immunoglobulin genes or fragments of immunoglobulin genes. The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon, and mu constant region genes, as well as the myriad of immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively.

The basic immunoglobulin (antibody) structural unit is generally a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" (about 50-70 kDa) chain. The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms "variable light chain" (V_L) and "variable heavy chain" (V_H) refer, respectively, to these light and heavy chains.

As used herein, the term "antibodies" includes intact immunoglobulins as well as a number of well-characterized fragments. For instance, Fabs, Fvs, and single-chain Fvs (scFvs) that bind to target protein (or epitope within a protein or fusion protein) would also be specific binding agents for that protein (or epitope). These antibody fragments are defined as follows: (1) Fab, the fragment which contains a monovalent antigen-binding fragment of an antibody molecule produced by digestion of whole antibody with the enzyme papain to yield an intact light chain and a portion of one heavy chain; (2) Fab', the fragment of an antibody molecule obtained by treating whole antibody with pepsin, followed by reduction, to yield an intact light chain and a portion of the heavy chain; two Fab' fragments are obtained per antibody molecule; (3) $(Fab')_2$, the fragment of the antibody obtained by treating whole antibody with the enzyme pepsin without subsequent reduction; (4) $F(ab')_2$, a dimer of two Fab' fragments held together by two disulfide bonds; (5) Fv, a genetically engineered fragment containing the variable region of the light chain and the variable region of the heavy chain expressed as two chains; and (6) single chain antibody, a genetically engineered molecule containing the variable region of the light chain, the variable region of the heavy chain, linked by a suitable polypeptide linker as a genetically fused single chain molecule. Methods of making these fragments are routine (see, for example, Harlow and Lane, *Using Antibodies: A Laboratory Manual*, CSHL, New York, 1999).

Antibodies for use in the methods and devices of this disclosure can be monoclonal or polyclonal. Merely by way of example, monoclonal antibodies can be prepared from murine hybridomas according to the classical method of Kohler and Milstein (*Nature* 256:495-97, 1975) or derivative methods thereof. Detailed procedures for monoclonal antibody production are described in Harlow and Lane, *Using Antibodies: A Laboratory Manual*, CSHL, New York, 1999.

Antibody binding affinity: The strength of binding between a single antibody binding site and a ligand (e.g., an antigen or epitope). The affinity of an antibody binding site X for a ligand Y is represented by the dissociation constant (K_d), which is the concentration of Y that is required to occupy half of the binding sites of X present in a solution. A smaller K_d indicates a stronger or higher-affinity interaction between X and Y and a lower concentration of ligand is needed to occupy the sites. In general, antibody binding affinity can be affected by the alteration, modification and/or substitution of one or more amino acids in the epitope recognized by the antibody paratope. In one example, antibody binding affinity is measured by end-point titration in an Ag-ELISA assay.

Antigen: A compound, composition, or substance that can stimulate the production of antibodies or a T-cell response in an animal, including compositions that are injected or absorbed into an animal. An antigen reacts with the products of specific humoral or cellular immunity, including those induced by heterologous immunogens. In one embodiment, an antigen is a virus antigen, such as a flavivirus E protein.

Biological sample: A sample obtained from a subject (such as a human or veterinary subject). Biological samples, include, for example, fluid, cell and/or tissue samples. In some embodiments herein, the biological sample is a fluid sample. Fluid sample include, but are not limited to, serum, blood, plasma, urine, feces, saliva, cerebral spinal fluid (CSF) and bronchoalveolar lavage (BAL) fluid.

Capsid protein (C protein): A flavivirus structural protein that functions to package viral RNA into the nucleocapsid core during virus assembly. The C-terminal portion of the C protein includes an internal signal sequence (referred to herein as either C(ss) or prM signal sequence) for translocation of the prM protein into the endoplasmic reticulum, where cleavage of the C and prM proteins occurs. This signal sequence varies in length among different flaviviruses. For example, the C(ss) of both WNV and ZIKV is 18 amino acids, while the C(ss) of DEN viruses is 14 amino acids.

Chimera: A molecule (e.g., nucleic acid or protein) composed of parts that are of different origin (such as at least two nucleic acids or polypeptides) that, while typically unjoined in their native state, are joined or linked to form a single continuous molecule. A chimera may include nucleic acids or polypeptides that are joined end-to-end (for example, the amino-terminus of one sequence is joined to the carboxyl-terminus of a second sequence) or may include a sequence from one molecule that is embedded within that of another molecule (for example, the amino-terminus and carboxyl-terminus of the chimera are from one molecule, while an intervening sequence comes from another molecule).

A chimera may include a chimeric protein, for example a protein that is composed of amino acids from more than one protein. A chimera may also include a chimeric nucleic acid composed of nucleic acid sequences from more than one source, such as a chimeric nucleic acid which encodes a chimeric protein. In other examples, a chimera may include a chimeric genome, such as a flavivirus genome, which is composed of sequences from two or more flaviviruses. For example, a chimeric flavivirus genome may comprise nucleic acid sequences from more than one flavivirus genome, such as a West Nile virus and a Zika virus. In some examples, a chimeric flavivirus includes nucleic acids encoding one or more proteins from a first flavivirus and nucleic acids encoding one or more proteins from a second flavivirus. In particular examples, a chimeric flavivirus is composed of a nucleic acid encoding the non-structural proteins and a C protein or a portion thereof from a West Nile virus genome linked to a nucleic acid encoding a prM protein and E protein (and optionally a portion of a C protein) from a Zika virus genome.

Conservative substitution: A substitution of one amino acid residue in a protein sequence for a different amino acid residue having similar biochemical properties. Typically, conservative substitutions have little to no impact on the activity of a resulting polypeptide. For example, ideally, a flavivirus protein (such as a prM, E, or non-structural protein) including one or more conservative substitutions (for example 1-10, 2-5, or 10-20, or no more than 2, 5, 10, 20, 30, 40, or 50 substitutions) retains the structure and function of the wild-type protein. A polypeptide can be produced to contain one or more conservative substitutions by manipulating the nucleotide sequence that encodes that polypeptide using, for example, standard procedures such as site-directed mutagenesis or PCR. In one example, such variants can be readily selected for additional testing by infecting cells with a virus containing a variant protein and determining its ability to replicate, by producing virus containing a variant protein and determining its neurovirulence or neuroinvasion properties, and/or by testing antibody cross-reactivity.

Contacting: Placement in direct physical association; includes both in solid and liquid form. "Contacting" is often used interchangeably with "exposed." In some cases, "contacting" includes transfecting, such as transfecting a nucleic acid molecule into a cell. In other examples, "contacting" refers to incubating a molecule (such as an antibody) with a biological sample.

Control: A reference standard, for example a positive control or negative control. A positive control is known to provide a positive test result. A negative control is known to provide a negative test result. However, the reference standard can be a theoretical or computed result, for example a result obtained in a population.

Envelope glycoprotein (E protein): A flavivirus structural protein that mediates binding of flavivirus virions to cellular receptors on host cells. The flavivirus E protein is required for membrane fusion, and is the primary antigen inducing protective immunity to flavivirus infection. Flavivirus E protein affects host range, tissue tropism and viral virulence. The flavivirus E protein contains three structural and functional domains, DI-DIII. In mature virus particles the E protein forms head to tail homodimers lying flat and forming a dense lattice on the viral surface.

Flavivirus non-structural protein: There are seven non-structural (NS) proteins of a flavivirus, NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5, which are encoded by the portion of the flavivirus genome that is 3' to the structural proteins. NS1 has been implicated in RNA replication and has been shown to be secreted from infected mammalian cells (Post et al., *Virus Res.* 18:291-302, 1991; Mackenzie et al., *Virology* 220:232-240, 1996; Muylaert et al., *Virology* 222:159-168, 1996). NS1 can elicit strong humoral immune responses and is a potential vaccine candidate (Shlesinger et al., *J. Virol.* 60:1153-1155, 1986; Qu et al., *J. Gen. Virol.* 74:89-97, 1993). NS2 is cleaved into NS2A and NS2B. NS2A is involved in RNA replication and virus particle assembly and secretion and NS2B forms a complex with NS3 and functions as a cofactor for the NS3 protease, which cleaves portions of the virus polyprotein. NS3 also functions as an RNA helicase and is used to unwind viral RNA during replication (Li et al., *J. Virol.* 73:3108-3116, 1999). While the exact functions of NS4A and NS4B remain to be elucidated, they are thought to be involved in RNA replication and RNA trafficking (Lindenbach and Rice, In: *Fields Virology*, Knipe and Howley, eds., Lippincott, Williams, and Wilkins, 991-1041, 2001). Finally, the NS5 protein is an RNA-dependent RNA polymerase involved in genome replication (Rice et al., *Science* 229:726-733, 1985). NS5 also shows methyltransferase activity commonly found in RNA capping enzymes (Koonin, *J. Gen. Virol.* 74:733-740, 1993).

Flavivirus structural protein: The capsid (C), premembrane (prM), and envelope (E) proteins of a flavivirus are the viral structural proteins. Flavivirus genomes consist of positive-sense RNAs that are roughly 11 kb in length. The genome has a 5' cap, but lacks a 3' polyadenylated tail (Wengler et al., *Virology* 89:423-437, 1978) and is translated into one polyprotein. The structural proteins (C, prM, and E) are at the amino-terminal end of the polyprotein followed by the non-structural proteins (NS1-5). The polyprotein is cleaved by virus and host derived proteases into individual proteins. The C protein forms the viral capsid while the prM and E proteins are embedded in the surrounding envelope (Russell et al., *The Togaviruses: Biology, Structure, and Replication*, Schlesinger, ed., Academic Press, 1980). The E protein functions in binding to host cell receptors resulting in receptor-mediated endocytosis. In the low pH of the endosome, the E protein undergoes a conformational change causing fusion between the viral envelope and the endosomal membranes. The prM protein is believed to stabilize the E protein until the virus exits the infected cell, at which time prM is cleaved to the mature M protein (Reviewed in Lindenbach and Rice, In: *Fields Virology*, Knipe and Howley, eds., Lippincott, Williams, and Wilkins, 991-1041, 2001).

Fluorescent protein: A protein that emits light of a certain wavelength when exposed to a particular wavelength of light. Fluorescent proteins include, but are not limited to, green fluorescent proteins (such as GFP, EGFP, AcGFP1, Emerald, Superfolder GFP, Azami Green, mWasabi, TagGFP, TurboGFP and ZsGreen), blue fluorescent proteins (such as EBFP, EBFP2, Sapphire, T-Sapphire, Azurite and mTagBFP), cyan fluorescent proteins (such as ECFP, mECFP, Cerulean, CyPet, AmCyanl, Midori-Ishi Cyan, mTurquoise and mTFP1), yellow fluorescent proteins (EYFP, Topaz, Venus, mCitrine, YPet, TagYFP, PhiYFP, ZsYellow1 and mBanana), orange fluorescent proteins (Kusabira Orange, Kusabira Orange2, mOrange, mOrange2 and mTangerine), red fluorescent proteins (mRuby, mApple, mStrawberry, AsRed2, mRFPI, JRed, mCherry, HcRed1, mRaspberry, dKeima-Tandem, HcRed-Tandem, mPlum, AQ143, tdTomato and E2-Crimson), orange/red fluorescence proteins (dTomato, dTomato-Tandem, TagRFP, TagRFP-T, DsRed, DsRed2, DsRed-Express (TI) and DsRed-Monomer) and modified versions thereof.

Heterologous: Originating from a different genetic sources or species. For example, a chimeric nucleic acid including nucleic acid from two (or more) different genetic sources or from two (or more) otherwise separated segments of sequence from a single genetic source is considered a heterologous nucleic acid. Similarly, a polypeptide including peptides from two (or more) different proteins from a single genetic source or two (or more) proteins from different genetic sources (such as a fusion protein) is considered a heterologous polypeptide. For example, a nucleic acid comprising portions of a WNV genome operably linked to a nucleic acid comprising portions of a ZIKV genome is a heterologous nucleic acid. Similarly, a polypeptide including a WNV polypeptide or portion thereof linked to a ZIKV polypeptide or portion thereof is a heterologous polypeptide.

In another example of use of the term heterologous, a nucleic acid that is heterologous to a cell originates from an organism or species other than the cell in which it is expressed. In one specific, non-limiting example, a heterologous nucleic acid includes a flavivirus nucleic acid that is present or expressed in a bacterial cell (such as an *E. coli* cell) or in an algal, plant, insect (e.g. C6/36), or mammalian (e.g., Vero) cell. Methods for introducing a heterologous nucleic acid into bacterial, algal, plant, insect, and mammalian cells are well known in the art, including infection of a cell with a viral nucleic acid, or transformation with a nucleic acid, for example electroporation, lipofection, and particle gun acceleration.

Immune response: A response of a cell of the immune system, such as a B-cell, T-cell, macrophage or polymorphonucleocyte, to a stimulus such as an antigen. An immune response can include any cell of the body involved in a host defense response for example, an epithelial cell that secretes an interferon or a cytokine. An immune response includes, but is not limited to, an innate immune response or inflammation.

Immunize: To render a subject protected from an infectious disease, such as by vaccination.

Inactivated virus: A virus (such as a viral vaccine) that has been rendered incapable of replication in host cells (and is thus not virulent), but can elicit an immune response. Methods of inactivating a virus (such as a virus including a nucleic acid chimera described herein) include chemical treatment (for example, formaldehyde), physical treatment (such as heat), irradiation, or combinations thereof.

Isolated: An "isolated" or "purified" biological component (such as a nucleic acid, peptide, protein, protein complex, or particle) has been substantially separated, produced apart from, or purified away from other components in a preparation or other biological components in the cell of the organism in which the component occurs, that is, other chromosomal and extrachromosomal DNA and RNA, and proteins. Nucleic acids, peptides and proteins that have been "isolated" or "purified" thus include nucleic acids and proteins purified by standard purification methods. The term also embraces nucleic acids, peptides and proteins prepared by recombinant expression in a host cell, as well as chemically synthesized nucleic acids or proteins. The term "isolated" or "purified" does not require absolute purity; rather, it is intended as a relative term. Thus, for example, an isolated biological component is one in which the biological component is more enriched than the biological component is in its natural environment within a cell, or other production vessel. Preferably, a preparation is purified such that the biological component represents at least 50%, such as at least 70%, at least 90%, at least 95%, or greater, of the total biological component content of the preparation.

Light-emitting protein: Any protein that is capable of emitting light or inducing the emission of light by acting on a particular substrate. Light-emitting proteins include, for example, fluorescent proteins and bioluminescent proteins. Fluorescent proteins include, for example, green fluorescent proteins and variants thereof (including blue, cyan, yellow, orange and red fluorescent proteins) and phycobiliproteins, such as B-phycoerythrin (B-PE), R-phycoerythrin (R-PE) and allophycocyanin (APC). Bioluminescent proteins include, for example, aequorin and luciferase (which acts on the substrate luciferin to emit light).

Nucleic acid molecule: A polymeric form of nucleotides, which may include both sense and anti-sense strands of RNA, cDNA, genomic DNA, and synthetic forms and mixed polymers of the above. A nucleotide refers to a ribonucleotide, deoxynucleotide or a modified form of either type of nucleotide. The term "nucleic acid molecule" as used herein is synonymous with "nucleic acid" and "polynucleotide." A nucleic acid molecule is usually at least 10 bases in length, unless otherwise specified. The term includes single- and double-stranded forms of DNA. A polynucleotide may include either or both naturally occurring and modified nucleotides linked together by naturally occurring and/or non-naturally occurring nucleotide linkages.

Operably linked: A first nucleic acid is operably linked to a second nucleic acid when the first nucleic acid is placed in a functional relationship with the second nucleic acid. Generally, operably linked DNA sequences are contiguous and, where necessary to join two protein coding regions, in the same reading frame. Operably linked nucleic acids include a first nucleic acid contiguous with the 5' or 3' end of a second nucleic acid. In other examples, a second nucleic acid is operably linked to a first nucleic acid when it is embedded within the first nucleic acid, for example, where the nucleic acid construct includes (in order) a portion of the first nucleic acid, the second nucleic acid, and the remainder of the first nucleic acid.

Pharmaceutically acceptable carrier: The pharmaceutically acceptable carriers (vehicles) useful in this disclosure are conventional. *Remington: The Science and Practice of Pharmacy*, The University of the Sciences in Philadelphia, Editor, Lippincott, Williams, & Wilkins, Philadelphia, Pa., 21^{st} Edition (2005), describes compositions and formulations suitable for pharmaceutical delivery of one or more therapeutic compositions, such as a chimeric virus, and additional pharmaceutical agents.

In general, the nature of the carrier will depend on the particular mode of administration being employed. For instance, parenteral formulations usually comprise injectable fluids that include pharmaceutically and physiologically acceptable fluids such as water, physiological saline, balanced salt solutions, aqueous dextrose, glycerol or the like as a vehicle. For solid compositions (for example, powder, pill, tablet, or capsule forms), conventional non-toxic solid carriers can include, for example, pharmaceutical grades of mannitol, lactose, starch, or magnesium stearate. In addition to biologically-neutral carriers, pharmaceutical compositions to be administered can contain minor amounts of non-toxic auxiliary substances, such as wetting or emulsifying agents, preservatives, and pH buffering agents and the like, for example sodium acetate or sorbitan monolaurate.

Premembrane protein (prM protein): A flavivirus structural protein. The prM protein is an approximately 25 kDa protein that is the intracellular precursor for the membrane (M) protein. prM is believed to stabilize the E protein during transport of the immature virion to the cell surface. When the virus exits the infected cell, the prM protein is cleaved to the mature M protein, which is part of the viral envelope (Reviewed in Lindenbach and Rice, In: Fields Virology, Knipe and Howley, eds., Lippincott, Williams, and Wilkins, 991-1041, 2001).

Preventing, treating or ameliorating a disease: "Preventing" a disease refers to inhibiting the full development of a disease. "Treating" refers to a therapeutic intervention that ameliorates a sign or symptom of a disease or pathological condition after it has begun to develop. "Ameliorating" refers to the reduction in the number or severity of one or more signs or symptoms of a disease.

Purified: The term purified does not require absolute purity; rather, it is intended as a relative term. Thus, for example, a purified nucleic acid preparation is one in which the nucleic acid is more enriched than the nucleic acid is in its natural environment (such as within a cell) or in a preparation or production vessel. In other examples, a purified virus preparation is one in which the virus is more enriched than in a cell or organism, a preparation, or a production vessel. A purified nucleic acid or virus also includes one that is substantially free of undesired components, such as an inactivating agent. Preferably, a preparation is purified such that the nucleic acid or virus represents at least 50% of the total content of the preparation. In some embodiments, a purified preparation contains at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or more of the nucleic acid or virus.

Recombinant nucleic add: A nucleic acid molecule (or protein or virus) that is not naturally occurring or has a sequence that is made by an artificial combination of two otherwise separated segments of sequence. This artificial combination is accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook et al. (ed.), *Molecular Cloning: A Laboratory Manual,* 2^{nd} ed., vol. 1-3, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989. The term recombinant includes nucleic acids and proteins that have been altered solely by addition, substitution, or deletion of a portion of a natural nucleic acid molecule or protein.

Sequence identity: The similarity between two nucleic acid sequences, or two amino acid sequences, is expressed in terms of the similarity between the sequences, otherwise referred to as sequence identity. Sequence identity is frequently measured in terms of percentage identity (or similarity or homology); the higher the percentage, the more similar the two sequences are.

Methods of alignment of sequences for comparison are well known in the art. Various programs and alignment algorithms are described in: Smith and Waterman (*Adv. Appl. Math.,* 2:482, 1981); Needleman and Wunsch (*J. Mol. Biol.,* 48:443, 1970); Pearson and Lipman (*Proc. Natl. Acad. Sci.,* 85:2444, 1988); Higgins and Sharp (Gene, 73:237-44, 1988); Higgins and Sharp (*CABIOS,* 5:151-53, 1989); Corpet et al. (*Nuc. Acids Res.,* 16:10881-90, 1988); Huang et al. (*Comp. Appls. Biosci.,* 8:155-65, 1992); and Pearson et al. (*Meth. Mol. Biol.,* 24:307-31, 1994). Altschul et al. (*Nature Genet.,* 6:119-29, 1994) presents a detailed consideration of sequence alignment methods and homology calculations.

The alignment tools ALIGN (Myers and Miller, *CABIOS* 4:11-17, 1989) or LFASTA (Pearson and Lipman, *Proc. Natl. Acad. Sci.* 85:2444-2448, 1988) may be used to perform sequence comparisons (Internet Program © 1996, W. R. Pearson and the University of Virginia, "fasta20u63" version 2.0u63, release date December 1996). ALIGN compares entire sequences against one another, while LFASTA compares regions of local similarity. These alignment tools and their respective tutorials are available on the Internet at the NCSA website. Alternatively, for comparisons of amino acid sequences of greater than about 30 amino acids, the "Blast 2 sequences" function can be employed using the default BLOSUM62 matrix set to default parameters, (gap existence cost of 11, and a per residue gap cost of 1). When aligning short peptides (fewer than around 30 amino acids), the alignment should be performed using the "Blast 2 sequences" function, employing the PAM30 matrix set to default parameters (open gap 9, extension gap 1 penalties). The BLAST sequence comparison system is available, for instance, from the NCBI web site; see also Altschul et al., *J. Mol. Biol.,* 215:403-10, 1990; Gish and States, *Nature Genet.,* 3:266-72, 1993; Madden et al., *Meth. Enzymol.,* 266:131-41, 1996; Altschul et al., *Nucleic Acids Res.,* 25:3389-402, 1997; and Zhang and Madden, *Genome Res.,* 7:649-56, 1997.

Serum: The fluid portion of the blood that separates out from clotted blood. Serum contains many proteins, including antibodies, but does not contain clotting factors.

Subject: Living multi-cellular vertebrate organisms, a category that includes both human and non-human mammals (such as mice, rats, rabbits, sheep, horses, cows, and non-human primates).

Therapeutically effective amount: A quantity of a specified agent (such as a chimeric virus) sufficient to achieve a desired effect in a subject being treated with that agent. For example, this may be the amount of a virus vaccine useful for eliciting an immune response in a subject and/or for preventing infection by the virus. In the context of the present disclosure, a therapeutically effective amount of a Zika virus vaccine, for example, is an amount sufficient to increase resistance to, prevent, ameliorate, and/or treat infection caused by Zika virus in a subject without causing a substantial cytotoxic effect in the subject. The effective amount of a Zika virus vaccine (or Zika virus immunogenic composition) useful for increasing resistance to, preventing, ameliorating, and/or treating infection in a subject will be dependent on, for example, the subject being treated, the manner of administration of the therapeutic composition and other factors.

Transformed: A "transformed" cell is a cell into which has been introduced a nucleic acid molecule (such as a heterologous nucleic acid) by molecular biology techniques. The term encompasses all techniques by which a nucleic acid molecule might be introduced into such a cell, including transfection with viral vectors, transformation with plasmid vectors, and introduction of naked DNA by electroporation, lipofection, and particle gun acceleration.

Vaccine: A preparation of immunogenic material capable of stimulating an immune response, administered for the prevention, inhibition, amelioration, or treatment of infectious or other types of disease. The immunogenic material may include attenuated or inactivated (killed) microorganisms (such as bacteria or viruses), or antigenic proteins, peptides or DNA derived from them. An attenuated virus is a virulent organism that has been modified to produce a less virulent form, but nevertheless retains the ability to elicit antibodies and cell-mediated immunity against the virulent form. An inactivated (killed) virus is a previously virulent organism that has been inactivated with chemicals, heat, or other treatment, but elicits antibodies against the organism. Vaccines may elicit both prophylactic (preventative or protective) and therapeutic responses. Methods of administration vary according to the vaccine, but may include inoculation, ingestion, inhalation or other forms of administration. Vaccines may be administered with an adjuvant to boost the immune response.

Vector: A vector is a nucleic acid molecule allowing insertion of foreign nucleic acid without disrupting the ability of the vector to replicate and/or integrate in a host cell. A vector can include nucleic acid sequences that permit it to replicate in a host cell, such as an origin of replication. An insertional vector is capable of inserting itself into a host nucleic acid. A vector can also include one or more selectable marker genes and other genetic elements. An expression vector is a vector that contains the necessary regulatory sequences to allow transcription and translation of inserted gene or genes.

West Nile virus (WNV): A member of the virus family Flaviviridae and the genus Flavivirus. Other members of this genus include dengue virus, yellow fever virus, Japanese encephalitis virus (JEV), Zika virus and Spondweni virus. WNV was first isolated from a woman in the West Nile district of Uganda in 1937. The virus was later identified in birds in the Nile delta region in 1953. Human infections attributable to WNV have been reported in many countries for over 50 years. In 1999, a WNV circulating in Israel and Tunisia was imported into New York, producing a large and dramatic outbreak that spread throughout the continental United States in the following years. Human infection is most often the result of bites from infected mosquitoes, but may also be transmitted through contact with other infection animals, their blood or other tissues. Infection with WNV is asymptomatic in about 80% of infected people, but about 20% develop West Nile fever. Symptoms include fever, headache, fatigue, body aches, nausea, vomiting, swollen lymph glands and in some cases, a skin rash. Approximately 1 in 150 of infected individuals develop severe, neuroinvasive disease, such as encephalitis, meningitis or poliomyelitis. Treatment of WNV infection is supportive, such as administration of intravenous fluids, respiratory support and prevention of secondary infections. There is currently no approved vaccine available for humans.

Zika virus (ZIKV): A member of the virus family Flaviviridae and the genus Flavivirus. Other members of this genus include dengue virus, yellow fever virus, Japanese encephalitis virus (JEV), West Nile virus and Spondweni virus. ZIKV is spread by the daytime-active mosquitoes *Aedes aegypti* and *A. albopictus*. This virus was first isolated from a Rhesus macaque from the Zika Forest of Uganda in 1947. Since the 1950s, ZIKV has been known to occur within a narrow equatorial belt from Africa to Asia. The virus spread eastward across the Pacific Ocean in 2013-

2014, resulting in ZIKV outbreaks in Oceania to French Polynesia, New Caledonia, the Cook Islands, and Easter Island. In 2015, ZIKV spread to Mexico, Central America, the Caribbean and South America, where ZIKV has reached pandemic levels. Infection by ZIKV generally causes either no symptoms are mild symptoms, including mild headache, maculopapular rash, fever, malaise, conjunctivitis and joint pain. ZIKV causes symptoms in about 20% of infected individuals, and no deaths from the virus have yet been reported. However, ZIKV infection has been linked to the birth of microcephalic infants following maternal infection, as well an increase in cases of GBS. Reports have also indicated that ZIKV has the potential for human blood-borne and sexual transmission. ZIKV has also been found in human saliva and breastmilk. There are currently no available medical countermeasures for the treatment or prevention of Zika virus infection (Malone et al., *PLoS Negl Trop Dis* 10(3):e0004530, 2016).

III. West Nile/Zika Virus Chimeras

Although both ZIKV and WNV are flaviviruses, ZIKV replicates more slowly and to lower titers than WNV in cell cultures. This makes production of Zika viruses or viral antigens (for example for development of ZIKV vaccines) more difficult than for WNV. The chimeric West Nile/Zika viruses described herein contain ZIKV antigenic structures on the surface of the virus particles while retaining certain WNV features (such as replication to high titer). The disclosed chimeras can thus be used in the development of immunogenic compositions, such as inactivated virus vaccines, for eliciting an immune response to Zika viruses. Due to their fast and more robust growth than the wild type Zika viruses in cell cultures, these chimeras can be produced in large quantity more efficiently than the wild-type ZIKV for making inactivated virus. The chimeric viruses disclosed herein can also be used as a challenge virus to assess the efficacy of ZIKV candidate vaccines. Furthermore, the chimeric viruses can be used for more rapid and effective ZIKV diagnostic assays.

Disclosed herein are chimeric flaviviruses that include non-coding regions, a C protein, a portion of a prM signal sequence, and non-structural proteins, from WNV; and include a portion of a prM signal sequence, a prM protein and an E protein from ZIKV. Tables 1 and 2 below provide start and stop positions of the particular genes and proteins in exemplary West Nile and Zika viruses. These sequences can serve as reference sequences and may be used to identify particular nucleotide or amino acid positions that correspond to positions referred to in the chimeric nucleic acids disclosed herein, or proteins encoded by the chimeric nucleic acids disclosed herein, for example by producing an alignment of a chimera and one of the virus sequences provided herein.

TABLE 1

Start and stop positions of noncoding regions (NCRs), structural proteins and nonstructural proteins in WNV NY99 (Genbank Accession No. AF196835)

Region	Nucleotide start/stop position (SEQ ID NO: 17)	Amino acid start/stop position (SEQ ID NO: 18)
5' NCR	1-96	—
C	97-465	1-123
C(ss)	412-465	106-123
prM	466-966	124-290
M	742-966	216-290
E	967-2469	291-791
NS1	2470-3525	792-1143
NS2A	3526-4218	1144-1374
NS2B	4219-4611	1375-1505
NS3	4612-6468	1506-2124
NS4A	6469-6915	2125-2273
NS4B	6916-7680	2274-2528
NS5	7681-10395	2529-3433
Stop	10396-10398	—
3' NCR	10399-11029	—

TABLE 2

Start and stop positions of NCRs, structural proteins and nonstructural proteins in ZIKV strain R103451

Region	Nucleotide start/stop position (SEQ ID NO: 13)	Amino acid start/stop position (SEQ ID NO: 14)
5' NCR	1-107	—
C	108-473	1-122
C(ss)	420-473	105-122
prM	474-977	123-290
M	753-977	216-290
E	978-2489	291-794
NS1	2490-3545	795-1146
NS2A	3546-4223	1147-1372
NS2B	4224-4613	1373-1502
NS3	4614-6464	1503-2119
NS4A	6465-6914	2119-2269
NS4B	6915-7667	2270-2520
NS5	7668-10376	2521-3423
Stop	10377-10379	—
3' NCR	10380-100807	—

In some examples disclosed herein, the WNV genome used in the chimera is derived from a particular WNV strain, such as NY99 or KEN-3829. Additional WNV strains are known in the art (see, e.g., Ebel et al. *Emerg. Infect. Dis.* 7:650-653, 2001; American Type Culture Collection (ATCC) catalog numbers VR-82, VR-1267, VR-1507, VR-1510). In particular examples, the WNV genome is WN NY99, for example, SEQ ID NO: 17 (GenBank Accession No. AF196835, incorporated by reference as included in GenBank on Jun. 14, 2016), or with mutations as described in Kinney et al. (*J. Gen. Virol.* 87:3611-3622, 2006), U.S. Pat. No. 8,715,689 and/or PCT Publication No. WO 2015/196094, each of which are incorporated by reference herein in their entirety. In some examples, the WNV genome sequence is modified, for example to introduce restriction sites for cloning purposes. These modifications can be silent mutations (for example, nucleotide sequence changes that do not alter amino acid sequence) or they may change the amino acid sequence.

WNV genome sequences are publicly available. For example, GenBank Accession Nos. AF196835, AY278441, AF202541, AF404754, AF260967, AY660002, AF481864, AY268133, AF404757, AY268132, AF260969, AF317203, AY262283, AY490240, AF260968, AY603654, D00246, M12294, EU068667, AY765264, and AY277251 disclose WNV genomic nucleic acid sequences, all of which are incorporated by reference as included in GenBank on Jun. 14, 2016. In further examples, the WNV genome, or the non-coding regions, C protein and/or non-structural proteins of the WNV genome are at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a publicly available WNV genome sequence.

In the disclosed nucleic acid chimeras, the ZIKV genome can be from any strain of ZIKV, including an African genotype strain or an Asian genotype strain. In some embodiments, the ZIKV is an African genotype strain, such as MR-766. In other embodiments, the ZIKV is an Asian genotype strain, such as SPH2015, PRVABC59, R103451, P6-740 or FSS 13025. In some embodiments, the ZIKV genome is from strain R103451 (SEQ ID NO: 13). The ZIKV genome may be a wild type strain or an attenuated (or vaccine) strain. In some examples, the ZIKV genome sequence is modified, for example to introduce restriction sites for cloning purposes. These modifications can be silent mutations (for example, nucleotide sequence changes that do not alter amino acid sequence) or they may change the amino acid sequence.

ZIKV sequences are publicly available. For example GenBank Accession Nos. KU321639.1, KU955595.1, KU955594.1, KU955593.1, KU955592.1, KU955591.1, KU681082.3, KU681081.3 and KX247646.1, all of which are incorporated by reference as included in GenBank on Jun. 14, 2016. In additional examples, the ZIKV genome (or the C signal sequence, prM, and/or E protein from the ZIKV genome) are at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a publicly available ZIKV sequence.

In some examples, the disclosed WN/ZKV chimeras include one or more nucleic acid substitutions that result in an amino acid substitution that provides a desirable characteristic, for example, increased stability or replication in cell culture (such as Vero or C6/36 cells), or decreased infectivity or transmission in mosquitoes, compared to the unsubstituted virus or chimera.

The viruses containing the disclosed nucleic acid chimeras can readily be produced by replication in host cells in culture. Methods of producing viruses are well known in the art (see e.g. *Fields Virology*, Knipe and Howley, eds., Lippincott, Williams, and Wilkins, 2001; Flint et al., *Principles of Virology*, ASM Press, 2000). Host cell lines are generally selected to be easy to infect with virus or transfect with viral genomic RNA, capable of stably maintaining foreign RNA with an unarranged sequence, and have the necessary cellular components for efficient transcription, translation, post-translation modification, virus assembly, and secretion of the protein or virus particle. In addition, cells are typically those having simple media component requirements which can be adapted for growth in suspension culture. In some examples, the host cell line is a mammalian cell line that is adapted to growth in low serum or serum-free medium. Exemplary suitable host cell lines include Vero (monkey), C6/36 (mosquito), BHK21 (hamster), LLC-MK2 (monkey) SK6 (swine), L292 (mouse), HeLa (human), HEK (human), 2fTGH cells (human), HepG2 (human), and PDK (dog) cells. Suitable cell lines can be obtained from the American Type Culture Collection (ATCC), Manassas, Va.

In some examples, the disclosed chimeric WN/ZKV replicate in cell culture more rapidly than wild type Zika viruses. In some examples, plaques formed by WN/ZKV chimeric viruses form on cell cultures (such as Vero, LLC-MK2 or BHK21 cells) sooner than ZIKVs (such as at least one day, two days, three days, four days, or five days post-infection sooner). In other examples, WN/ZKV chimeric viruses form larger plaques than ZIKVs, for example, plaques that are at least 25% larger to about 10 times larger than Zika viruses (such as at least 50% larger, two-fold, three-fold, four-fold, five-fold, or up to 10-fold larger).

The disclosure also provides WN/ZKV chimeras having one or more nucleic acid or amino acid substitutions, insertions, deletions, or combinations thereof, such that the resulting chimera has improved characteristics. In some examples, the improved characteristic of the chimera includes but is not limited to increased virus titer, increased replication rate, increased plaque size, or increased stability in cell culture compared to a wild type virus. In additional examples, the improved characteristic of the chimera includes increased infectivity or virulence in a subject (such as mice or non-human primates) or decreased infectivity or transmissibility in mosquitoes as compared to a wild type virus. For example, to decrease infectivity or transmissibility in mosquitoes, the WN/ZKV chimeras may include one or more miRNAs specific to mosquito cells, such as but not limited to, miRNA-14, miRNA-184 or miRNA-1175.

Manipulation of the nucleotide sequence of the disclosed chimeric flaviviruses by standard procedures, including for instance site-directed mutagenesis or PCR and M13 primer mutagenesis, can be used to produce variants with improved characteristics (such as increased virus titer or stability in cell culture). Details of these techniques are well known. For instances, protocols are provided in Sambrook et al. (ed.), *Molecular Cloning: A Laboratory Manual*, 2^{nd} ed., vol. 1-3, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989. The simplest modifications involve the substitution of one or more amino acids for amino acids having similar physiochemical and/or structural properties. These so-called conservative substitutions are likely to have minimal impact on the activity and/or structure of the resultant protein. Conservative substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Examples of conservative substitutions are shown below.

Original Residue	Conservative Substitutions
Ala	Ser
Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
His	Asn; Gln
Ile	Leu, Val
Leu	Ile; Val
Lys	Arg; Gln; Glu
Met	Leu; Ile
Phe	Met; Leu; Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp; Phe
Val	Ile; Leu

The substitutions which in general are expected to produce the greatest changes in protein properties will be non-conservative, for instance changes in which (a) a hydrophilic residue, for example, seryl or threonyl, is substituted for (or by) a hydrophobic residue, for example, leucyl, isoleucyl, phenylalanyl, valyl or alanyl (or vice versa); (b) a cysteine or proline is substituted for (or by) any other residue; (c) a residue having an electropositive side chain, for example, lysyl, arginyl, or histadyl, is substituted for (or by) an electronegative residue, for example, glutamyl or asparty (or vice versa); or (d) a residue having a bulky side chain, for example, phenylalanine, is substituted for (or by) one not having a side chain, for example, glycine (or vice versa).

In addition to targeted mutagenesis to produce variants of the disclosed WN/ZKV chimeras, mutations may accrue upon passage in cell culture that result in variants, some with desirable characteristics. Nucleic acid and amino acid substitutions, insertions, and/or deletions that accrue in chimeric viruses during cell culture passages are readily determined by sequence analysis of the virus amplified from isolated plaques of the virus seed, and can be engineered into infectious clones to generate WN/ZKV chimera variants that have improved characteristics (such as replication to high titer or production of uniform large plaques in cells). Consistent mutations identified from multiple seeds or isolated plaques are one indication of a desirable substitution of the chimera in the cell type. Previous studies have successfully identified substitutions which occurred in cell culture and engineered these into different chimeric virus constructs to produce chimeric viruses with improved characteristics (e.g., Huang et al., *J. Virol.* 77:11436-11447, 2003; Huang et al., *J. Virol.* 12:7300-7310, 2005; U.S. Pat. No. 8,715,689; and WO 2015/196094).

A. Nucleic Acid Chimeras

Provided herein are flavivirus nucleic acid chimeras. In some embodiments, the nucleic acid chimera includes a first nucleic acid molecule comprising a 5' non-coding region, a nucleic acid encoding a C protein and non-structural proteins, and a 3' non-coding region, each from a West Nile virus genome, wherein the C protein comprises a portion of a prM signal sequence from the West Nile virus genome and a portion of a prM signal sequence from a Zika virus genome; and a second nucleic acid molecule operably linked to the first nucleic acid molecule, encoding a prM protein and an E protein from the Zika virus genome.

In some examples, the portion of the prM signal sequence from the West Nile virus genome includes the first 15 amino acids of the West Nile virus prM signal sequence and the portion of the prM signal sequence from the Zika virus genome includes the last three amino acids of the Zika virus prM signal sequence. In specific non-limiting examples, the first 15 amino acids of the West Nile virus prM signal sequence includes amino acids 106-120 of SEQ ID NOs: 2 and 4 and/or the last three amino acids of the Zika virus prM signal sequence includes AMA (amino acids 121-123 of SEQ ID NOs: 2 and 4).

In other examples, the portion of the prM signal sequence from the West Nile virus genome includes the first 13 amino acids of the West Nile virus prM signal sequence and the portion of the prM signal sequence from the Zika virus genome includes the last five amino acids of the Zika virus prM signal sequence. In specific non-limiting examples, the first 13 amino acids of the West Nile virus prM signal sequence includes amino acids 106-118 of SEQ ID NO: 6 and/or the last five amino acids of the Zika virus prM signal sequence includes amino acids 119-123 of SEQ ID NO: 6.

In yet other examples, the portion of the prM signal sequence from the West Nile virus genome includes the first three amino acids of the West Nile virus prM signal sequence and the portion of the prM signal sequence from the Zika virus genome includes the last 15 amino acids of the Zika virus prM signal sequence. In specific non-limiting examples, the first three amino acids of the West Nile virus prM signal sequence includes amino acids GGK (amino acids 106-108 of SEQ ID NO: 8) and/or the last 15 amino acids of the Zika virus prM signal sequence includes amino acids 109-123 of SEQ ID NO: 8.

In some embodiments, the West Nile virus is strain NY99 or KEN-3829.

In some embodiments, the Zika virus is an African genotype virus, such as strain MR-766. In other embodiments, the Zika virus is an Asian genotype virus, such as strain SPH2015, PRVABC59, R103451, P6-740 or FSS 13025.

In some embodiments, the nucleic acid chimera includes a nucleic acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7. In some examples, the nucleic acid chimera includes the nucleic acid sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7.

In some embodiments, the nucleic acid chimera encodes an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8. In some examples, the nucleic acid chimera encodes the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8.

In some embodiments, the nucleic acid chimera further includes a reporter gene. In some examples, the reporter gene encodes a light-emitting protein. In some examples, the light-emitting protein is a fluorescent protein, such as a green, blue, cyan, yellow, orange or red fluorescent protein. In other examples, the light-emitting protein is a bioluminescent protein, such as luciferase. In particular non-limiting examples, the reporter gene encodes a green fluorescent protein, such as ZsGreen or mWasabi.

In some examples, the reporter gene is inserted upstream (5') of a complete C gene, and an additional nucleic acid sequence encoding a portion of the C protein (such as the first 25 or 35 amino acids of the C protein) is inserted between the 5' non-coding region and the reporter gene (see FIG. **2**, Type I reporter construct). In specific non-limiting examples, the nucleic acid sequence encoding the portion of the C protein is human codon optimized or modified with multiple silent mutations to enhance the genetic stability of the reporter virus by decreasing homologous sequences between the complete and partial C genes. In particular examples, the nucleic acid sequence of the reporter gene (such as ZsGreen) is human codon optimized.

In some examples, a nucleic acid sequence encoding a self-cleaving 2A peptide (such as F2A or P2A) is placed at the 3' end of the reporter gene (see FIG. **2**, Type II reporter construct). In particular examples, the reporter gene and 2A peptide coding sequence are inserted in the signal sequence region at the 3' end of the C gene. In specific non-limiting examples, the reporter gene and 2A peptide coding sequence are flanked by a nucleic acid sequence encoding the first three amino acids (GGK) of the WNV signal sequence at the 5' end and a nucleic acid sequence encoding the 18 amino acid ZIKV signal sequence at the 3' end (see FIG. **2**, Type II reporter construct).

In some examples, the nucleic acid sequence encoding the report construct is human codon optimized.

In some examples, the nucleic acid chimera includes a nucleic acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 19. In specific examples, the nucleic acid chimera includes the nucleic acid sequence of SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 19.

In some examples, the nucleic acid chimera encodes an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 20. In specific examples, the nucleic acid chimera encodes the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 20.

Also provided herein are chimeric flaviviruses that comprise a nucleic acid chimera disclosed herein. Compositions, such as immunogenic compositions, that include the chimeric flaviviruses are also provided by the present disclosure.

B. Inactivated Virus, Methods of Use and Methods of Making

Further provided herein are inactivated chimeric flaviviruses. In particular, provided are chimeric West Nile/Zika viruses that have been inactivated using any method known to one of skill in the art. The chimeric West/Nile Zika viruses have a chimeric nucleic acid that includes a first nucleic acid molecule comprising a 5' non-coding region, a nucleic acid encoding a C protein and non-structural proteins, and a 3' non-coding region, each from a West Nile virus genome, wherein the C protein comprises a portion of a prM signal sequence from the West Nile virus genome and a portion of a prM signal sequence from a Zika virus genome; and a second nucleic acid molecule operably linked to the first nucleic acid molecule, encoding a prM protein and an E protein from the Zika virus genome, as described in the above section.

Also provided are immunogenic compositions that include an inactivated flavivirus comprising a nucleic acid chimera disclosed herein and a pharmaceutically acceptable carrier. In some embodiments, the inactivated virus is purified.

In some embodiments, the inactivated virus is inactivated by one or more of chemical inactivation, high pressure inactivation, ultraviolet or gamma irradiation, or any combination thereof.

Further provided herein is a method of eliciting an immune response against Zika virus in a subject by administering to the subject an inactivated virus or immunogenic composition disclosed herein. The immune response may include, for example, induction of ZIKV-specific antibodies (such as IgM and/or IgG antibodies) or induction of a virus-specific T cell response. In some examples, the immune response is a protective immune response.

In some embodiments, the subject is a human.

In some embodiments, the method includes administering one to five doses (such as 1, 2, 3, 4 or 5 doses) of the immunogenic composition to the subject. In some examples, the method further includes administering one or more adjuvants to the subject.

Also provided is a method of immunizing a subject against ZIKV by administering to the subject an inactivated virus or immunogenic composition disclosed herein. In some embodiments, the subject is a human.

Further provided is a method that includes inactivating a virus that includes a nucleic acid chimera disclosed herein. In some embodiments, inactivating the virus includes treating the virus with a chemical inactivation agent, high pressure, ultraviolet irradiation, gamma irradiation, or any combination thereof. In some examples, the method further includes purifying the inactivated virus. In some examples, the method further includes administering the inactivated virus to a subject

C. Methods of Detecting Zika Virus Infection

Methods of detecting ZIKV-specific antibodies in a sample are also provided herein. In some embodiments, the method includes contacting the sample with a chimeric virus disclosed herein under conditions sufficient to form virus-antibody complexes if ZIKV antibodies are present in the sample; and detecting the virus-antibody complexes, thereby detecting ZIKV-specific antibodies in the sample.

In some embodiments, the method includes contacting the sample with a chimeric virus disclosed herein to form a virus-sample mixture, wherein virus-antibody complexes are formed in the virus-sample mixture if ZIKV-specific antibodies are present in the sample; inoculating a cell culture with the virus-sample mixture under conditions sufficient to allow plaque formation or micro-focus formation in the cell culture; and detecting a decrease in plaque formation or micro-focus formation in the cell culture as compared to a virus-infected control cell culture.

In some embodiments, the method includes providing a chimeric virus disclosed herein bound to a solid support; contacting the chimeric virus-bound solid support with the sample under conditions sufficient to form virus-antibody complexes if ZIKV-specific antibodies are present in the sample; contacting the virus-antibody complexes with a secondary antibody; and detecting binding of the secondary antibody to the virus-antibody complexes.

In some embodiments, the method includes providing a secondary antibody bound to a solid support; contacting the secondary antibody-bound solid support with the sample under conditions sufficient to allow binding of the secondary antibody to any ZIKV-specific antibodies present in the sample, thereby forming antibody-antibody complexes; contacting the antibody-antibody complexes with a chimeric virus disclosed herein under conditions sufficient for the chimeric virus to bind the ZIKV-specific antibodies, thereby forming immune complexes; and detecting the presence of the immune complexes. In some examples, detecting the presence of the immune complexes includes contacting the immune complexes with an antibody that specifically binds the chimeric virus and comprises a detectable label.

In some embodiments, the method includes providing a ZIKV-specific antibody bound to a solid support; contacting the antibody-bound solid support with a chimeric virus disclosed herein under conditions sufficient for the chimeric virus to bind the ZIKV-specific antibody to form antibody-virus complexes; contacting the antibody-virus complexes with the sample to allow binding of any ZIKV-specific antibodies present in the sample to the chimeric virus, thereby forming immune complexes; contacting the immune complexes with a secondary antibody; and detecting binding of the secondary antibody to the immune complexes, thereby detecting ZIKV-specific antibodies present in the sample.

In some examples of the detection methods, the secondary antibody is an anti-IgM antibody. In other examples, the secondary antibody is an anti-IgG antibody. In specific examples, the secondary antibody includes an anti-human IgM antibody or an anti-human IgG antibody.

In some examples, the sample includes a biological fluid samples, such as serum, blood or plasma. In particular non-limiting examples, the sample includes serum.

In some examples, the ZIKV-specific antibody is cross-reactive with other flaviviruses.

In some examples, the ZIKV-specific antibody is a neutralizing antibody.

IV. Compositions and Methods for Eliciting an Immune Response

Due to its robust replication in Vero cells, the chimeric viruses disclosed herein can be readily utilized for producing inactivated virus vaccine from vaccine-production certified Vero cells. Inactivated flavivirus vaccines, such as Japanese encephalitis virus vaccine and tick-borne encephalitis vaccine, have previously been used successfully in humans. An inactivated ZIKV vaccine may be a safe vaccine option for pregnant woman to prevent ZIKV-caused microcephaly in the fetus. Large quantities of virus are required for purification and inactivation procedures to make an inactivated vaccine. Thus, the chimeric West Nile/Zika viruses disclosed herein are advantageous due to their ability to produce very high titers for many days, which will significantly enhance Zika virus vaccine production.

Provided herein are methods of eliciting an immune response in a subject by administering an inactivated viruses including a WN/ZKV chimeric nucleic acid to the subject. In a particular example, the subject is a human. The inactivated virus comprising a WN/ZKV nucleic acid chimera is used to produce an immune response that prevents or inhibits infection with a ZIKV, and can also be used to treat or inhibit infection with ZIKV.

In some examples, the method further includes selecting a subject in need of enhanced immunity to ZIKV. Subjects in need of enhanced immunity to ZIKV include subjects who are at risk of ZIKV infection, and subjects who have been previously vaccinated with a ZIKV vaccine. Residents of, or travelers to, countries or regions where ZIKV is endemic are at risk of contracting ZIKV. Additional factors that contribute to risk of infection with ZIKV include the characteristics of the area, presence of ZIKV in the area, exposure to mosquitos, and lack of preventive measures (such as insect repellant).

In some examples, the chimeric virus is inactivated, for example, using chemical inactivation, high pressure inactivation, ultraviolet or gamma irradiation, or any combination thereof. For example, chemical inactivation includes exposing the virus to one or more of formaldehyde (e.g., formalin), β-propiolactone, aziridines, hydrogen peroxide, organic solvents, surfactants (e.g., sarkosyl) or non-ionic detergents (e.g., Triton®-X100), or ascorbic acid for a time sufficient to inactivate the virus. In one example, the virus is inactivated using an oxidizing agent such as hydrogen peroxide, for example, treatment with about 0.05-5% hydrogen peroxide (such as about 0.1-1% about 0.5-3%, about 1-5%) at room temperature for about 1-24 hours (such as about 1-16 hours, about 2-12 hours, about 4-8 hours, about 1-6 hours, for example, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 6 hours, about 8 hours, about 12 hours, about 16 hours, or about 24 hours). See, e.g., WO 2008/039171; Amanna et al., *Nat. Med* 18:974-979, 2012; Pinto et al., *J. Virol.* 87:1926-1936, 2013. One of ordinary skill in the art can determine optimal hydrogen peroxide concentrations and conditions for inactivation for different starting viral titers or volumes.

In a particular, non-limiting example, the virus is treated with about 0.001-0.5% sarkosyl (such as about 0.005-0.4%, about 0.025-0.2%, or about 0.01-0.4% sarkosyl, for example, about 0.005%, about 0.01%, about 0.025%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, or about 0.5% sarkosyl) at about 20-37° C. (for example, about 20-37° C., about 22-30° C., about 30-37° C., or about room temperature) for a sufficient time to inactivate the virus (such as about 15 minutes to 3 hours, about 30 minutes to 2 hours, about 1-2 hours or about 30 minutes to 90 minutes). One of ordinary skill in the art can determine optimal detergent concentrations and conditions for inactivation for other detergents and/or different starting viral titers or volumes. In some examples, longer inactivation times are used at lower temperatures (such as room temperature) than at higher temperatures (such as 37° C.). One of ordinary skill in the art can determine inactivation times based on the temperature of treatment and routine experimentation.

In other examples, the virus is exposed to an ultraviolet light source (such as a UV-C light source of 254 nm) or a radioactive source (such as cobalt-60) for a time sufficient to inactivate the virus. In some examples, the virus (such as a WN/ZIKV chimera disclosed herein) is exposed to about 350-700 $\mu W/cm^2$ (such as about 350-680 $\mu W/cm^2$, about 400-670 $\mu W/cm^2$, about 670-685 $\mu W/cm^2$, or about 350 $\mu W/cm^2$, about 670 $\mu W/cm^2$, or about 680 $\mu W/cm^2$) of UV-254 nm for about 10 minutes to 2 hours (such as about 15 minutes to 1 hour, about 15-45 minutes, about 1-2 hours, about 15 minutes, about 30 minutes, about 45 minutes, about 1 hour, or more). In other examples, the virus is exposed to about 0.1-200 mW/cm^2 (such as about 0.5-5 mW/cm^2, about 1-10 mW/cm^2, about 10-50 mW/cm^2, about 25-100 mW/cm^2, about 100-200 mW/cm^2, for example, about 2 mW/cm^2, about 5 mW/cm^2, about 10 mW/cm^2, about 50 mW/cm2, about 100 mW/cm^2, about 150 mW/cm^2, or about 200 mW/cm^2) for about 10 minutes to 8 hours (such as about 30 minutes to 1 hour, about 1-6 hours, about 2-4 hours, about 15 minutes, about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 6 hours, about 8 hours). In some examples, the virus in kept cool (for example at 4° C. or on ice) during UV treatment. In particular examples, small volumes (such as less than about 1 ml) are treated at 670 $\mu W/cm^2$ for 15 minutes or 350 $\mu W/cm^2$ for 45 minutes and larger volumes (such as about 1 ml or more, for example about 2-5 ml, about 1-3 ml, or more) are treated at 680 $\mu W/cm^2$ for 45 minutes or more. One of ordinary skill in the art can determine optimal UV power and conditions for inactivation for other volumes or different starting viral titers.

In additional examples, the virus is inactivated by photochemical inactivation. The methods include exposure of the virus to UV radiation (365 nm) in the presence of photo-activatable chemicals, such as 1,5-indonaphthylazide (INA), 4'-aminomethyl-trioxsalen (AMT), 8-methoxypsoralen (MOP), 4,5',8-trimethylpsoralen (TMP), or psoralen. See, e.g., Raviprakash et al., *Hum Vaccines Immunother.* 9:2336-2341, 2013; Raviv et al., *J. Virol.* 82:4612-4619, 2008; Sharma et al., *Vaccine* 29:953-959, 2011; Hanson et al., *J. Gen. Virol.* 40:345-358, 1978. In particular examples, the virus is exposed to about 0.1-200 mW/cm^2 (such as about 0.1-1 mW/cm^2, about 0.5-5 mW/cm^2, about 1-100 mW/cm^2, about 100-200 mW/cm^2, for example, about 2 mW/cm^2, about 100 mW/cm^2, about 145 mW/cm^2, about 180 mW/cm^2, or about 200 mW/cm^2) of UV-365 nm for about 1 minute to about 6 hours (such as about 2-15 minutes, about 5-30 minutes, about 15 minutes to 1 hour, about 15-45 minutes, about 1-2 hours, about 90 minutes to 4 hours, about 2-6 hours, about 2 minutes, about 5 minutes, about 10 minutes, about 15 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 2 hours, about 4 hours, about 6 hours, or more) in the presence of INA, ANT, MOP, TMP, or psoralen. One of ordinary skill in the art can determine optimal UV power and conditions for inactivation using particular compounds, virus volumes, or starting viral titers.

Before or after the chimeric virus has been inactivated, the virus may be purified. Purification methods include filtration or diafiltration, chromatography (e.g., size exclusion, ion exchange, or immunoaffinity chromatography), density-gradient centrifugation, glycerol-cushion centrifugation, or Cellufine® sulfate media chromatography. In other examples, the chimeric virus is purified prior to inactivation. If purified virus is inactivated, an additional purification step may be included following inactivation, for example, to remove a chemical inactivation agent (such as detergent), for example using filtration or buffer exchange. Preparations of purified inactivated WN/ZIKV chimeras may include both inactivated whole virus and inactivated virus-like particles.

In some examples, chimeras are purified (for example, through polyethylene glycol 8000 (PEG8000) precipitation and gradient-density centrifugation, glycerol cushion centrifugation, and/or Cellufine® sulfate media chromatography) before inactivation. Inactivated viruses may be further purified by filtration to remove inactivating reagent, for example, if necessary. In particular examples, detergent (such as sarkosyl) is removed after inactivation by filtration, detergent removal spin columns (such as Millipore Detergent-OUT™ kits), dialysis, or ion-exchange chromatography. Final product may be tested for infectivity in cell cultures, antigenicity (for example, by ELISA; as discussed in Section VI, below), and/or protein concentration (for example, by Bradford or bicinchoninic acid protein assay).

One or more purified inactivated viruses comprising a WN/ZKV nucleic acid chimera (for example in the form of a pharmaceutical or immunogenic composition) are administered to a subject by any of the routes normally used for introducing a composition into a subject. Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, parenteral, intravenous, subcutaneous, vaginal, rectal, intranasal, inhalation or oral. Parenteral administration, such as subcutaneous, intravenous or intramuscular administration, is generally achieved by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described. Administration can be systemic or local.

Immunogenic compositions are administered in any suitable manner, such as with pharmaceutically acceptable carriers. Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. See, e.g., *Remington: The Science and Practice of Pharmacy*, The University of the Sciences in Philadelphia, Editor, Lippincott, Williams, & Wilkins, Philadelphia, Pa., 21st Edition (2005). Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions of the present disclosure.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like.

In some examples, the compositions disclosed herein include one or more adjuvants. In other examples, an adjuvant is not included in the composition, but is separately administered to a subject (for example, in combination with a composition disclosed herein) before, after, or substantially simultaneously with administration of one or more of the compositions disclosed herein. Adjuvants are agents that increase or enhance an immune response in a subject administered an antigen, compared to administration of the antigen in the absence of an adjuvant. One example of an adjuvant is an aluminum salt, such as aluminum hydroxide, aluminum phosphate, aluminum potassium sulfate, or aluminum hydroxyphosphate. Other adjuvants include biological adjuvants, such as cytokines (for example, IL-2, IL-6, IL-12, RANTES, GM-CSF, TNF-α, or IFN-γ), growth factors (for example, GM-CSF or G-CSF), one or more molecules such as OX-40L or 4-1 BBL, immunostimulatory oligonucleotides (for example, CpG oligonucleotides), Toll-like receptor agonists (for example, TLR2, TLR4, TLR7/8, or TLR9 agonists), and bacterial lipopolysaccharides or their derivatives (such as 3D-MPL). Additional adjuvants include oil and water emulsions, squalene, or other agents. In one example, the adjuvant is a mixture of stabilizing detergents, micelle-forming agent, and oil available under the name PROVAX® (IDEC Pharmaceuticals, San Diego, Calif.). One of skill in the art can select a suitable adjuvant or combination of adjuvants to be included in the compositions disclosed herein or administered to a subject in combination with the compositions disclosed herein.

Administration is accomplished by single or multiple doses. The dose administered to a subject in the context of the present disclosure should be sufficient to induce a beneficial therapeutic response in a subject over time, or to inhibit or prevent ZIKV infection. The dose required will vary from subject to subject depending on the species, age, weight and general condition of the subject, the severity of the infection being treated, the particular immunogenic composition being used, and its mode of administration. An appropriate dose can be determined by one of ordinary skill in the art using only routine experimentation. In some examples, the dose of inactivated virus (such as in an immunogenic composition) administered to the subject is about 0.1 μg to about 100 μg. For example, a dose of the immunogenic composition can contains at least 0.1 μg, at least 0.2 μg, at least 0.25 μg, at least 0.3 μg, at least 0.33 μg, at least 0.4 μg, at least 0.5 μg, at least 1.0 μg, at least 2.0 μg, at least 3.0 μg, at least 5.0 μg, at least 10.0 μg, at least 20 μg, at least 40 μg, at least 80 μg, or at least 100 μg (or any amount between 0.1 and 10.0 μg) of inactivated chimeric virus.

Repeated immunizations may be necessary to produce an immune response in a subject. When administered in multiple doses, the booster doses are administered at various time intervals, such as weeks or months to years. In other examples, the inactivated WN/ZKV chimeric viruses are used as a booster following administration of one or more ZIKV vaccines. In one example, a subject is administered a prime dose of a live-attenuated ZIKV vaccine followed by at least one boost dose of the inactivated WN/ZKV chimeric viruses disclosed herein. In some examples, the boost dose is administered about 14, 30, 60, 90, or more days after administration of the prime dose. Additional boosters (of live-attenuated ZIKV or inactivated WN/ZKV chimeras) can be administered at subsequent time points, if determined to be necessary or beneficial. Immunization protocols (such as amount of immunogen, number of doses and timing of administration) can be determined experimentally, for example by using animal models (such as mice or non-human primates), followed by clinical testing in humans.

V. Preparation of Viruses

Methods of cell culture, viral replication, plaque titration, and virus or virus particle purification are well known in the art. See e.g. Obijeski et al., *J. Gen. Virol.* 22:21-33, 1974; Beaty et al., *Diagnostic Procedures for Viral, Ricksettial, and Chlamydial Infections*, pp. 189-212, Lennette et al. (eds.), 7^{th} Edition, American Public Health Association, 1995; *Virology Methods Manual*, Mahy and Kangro (eds.), Academic Press, 1996.

The chimeric viruses of the present disclosure can be made using standard methods known and recognized in the art. For example, an RNA molecule corresponding to the genome of a virus, or a chimeric virus, can be introduced into primary cells, chick embryos, or diploid cell lines, from which (or the supernatants of which) progeny virus can then be purified. Another method that can be used to produce the viruses employs heteroploid cells, such as Vero cells (Yasumura et al., *Nihon Rinsho* 21:1201-1215, 1963) or C6/36 cells. In this method, a nucleic acid molecule (e.g., an RNA molecule) corresponding to the genome of a virus or chimeric virus is introduced into the heteroploid cells and virus is harvested from the medium in which the cells have been cultured. The harvested virus can be further amplified in cell cultures and then concentrated (e.g., by PEG 8000 precipitation, use of ultrafiltration, such as a filter having a molecular weight cut-off of, e.g., 50-500 kDa (e.g., Amicon ultracentrifugal filter, tangential flow filtration cassette, or Pellicon-2 Mini ultrafilter cassette)), diafiltered against MEME without phenol red or FBS, formulated by the addition of lactose, and filtered into a sterile container. Details of a method of virus production are provided in WO 03/060088. Viruses optionally are further purified, for example by density gradient centrifugation, glycerol cushion centrifugation, and/or Cellufine® sulfate media chromatography.

VI. Detection of Flavivirus Antibodies

The present disclosure further provides a method of detecting a Zika virus-reactive antibody in a sample (such as a sample from a subject, for example, a blood or serum sample), including contacting the sample with a chimeric virus disclosed herein under conditions sufficient to form virus-antibody complexes if Zika virus antibodies are present in the sample; and detecting formation of the complexes, thereby detecting Zika virus antibody in the sample. An advantage of the disclosed WN/ZKV chimeras is that they grow faster and to higher titers and produce larger and more well-defined plaques or micro-foci than wild type ZIKV. It is disclosed herein that chimeric WN/ZIKV expresses authentic ZIKV neutralization epitopes that result in neutralization assay results that are equivalent to the neutralization assay using wt ZIKV (Table 3). In addition, the chimeric virus can speed up the traditional PRNT from 5-6 days to 3-4 days, and plaque morphology of the WN/ZIKV is more uniform for consistent counting. Therefore, the disclosure provides methods of detecting ZIKV-reactive antibody in a sample that are faster and more accurate (consistent) than methods utilizing wild type ZIKV.

The methods of detecting Zika virus-specific antibodies in a sample are performed, for example, by contacting a fluid or tissue sample from a subject with a chimeric virus of this disclosure and detecting the binding of at least one polypeptide encoded by the virus to the antibody. A fluid sample of this method includes any biological fluid which could contain the antibody, such as cerebrospinal fluid, blood, bile plasma, serum, saliva and urine. Other possible examples of body fluids include sputum, mucus and the like.

In one example, the presence of a ZIKV antibody is detected in a sample from a subject utilizing a disclosed chimeric flavivirus in a plaque-reduction neutralization test (PRNT) or micro-focus reduction neutralization test (mFRNT). In the PRNT or mFRNT assay, a sample is contacted with a virus encoded by a chimeric flavivirus disclosed herein. A suitable cell culture (such as Vero, C6/36, LLC-MK2 or BHK cells) is inoculated with the virus-sample mixture to infect the cells. The cell culture is incubated under conditions sufficient to allow plaque or micro-focus formation and the number of plaques or micro-foci formed in a culture inoculated with the chimeric virus-sample mixture is compared to the number of plaques or micro-foci formed in a control culture (such as cells inoculated with virus alone). A reduction in the number of plaques or micro-foci in the cell culture inoculated with the chimeric virus-sample mixture as compared to the control culture (for example a decrease of at least 50%, 60%, 70%, 80%, 90%, 95%, or 99% compared with the control sample) indicates the presence of a ZIKV antibody, such as a neutralizing antibody, in the sample.

Chimeric WN/ZKVs encoding a fluorescent reporter (ZsGreen) are also disclosed herein (referred to as WN/ZKV-ZsG0 and WN/ZKV-ZsG1). The reporter viruses can be used to improve the micro-neutralization assay because the viral foci (infected cells) can be directly imaged and automatically counted, for example, by an ELISPOT reader. This eliminates the time-consuming and labor-intensive procedure required for immunostaining of viral foci.

The robust growth characteristics of the chimeric virus disclosed herein can also be useful in the production of ZIKV particles for use in a variety of diagnostic assays. For example, viral particles and/or antigens are required in various serology assays, such as traditional IgM antibody capture (MAC)-ELISA or IgG antibody capture (GAC)-ELISA, indicted ELISA and rapid lateral flow assays. Other immunoassays, such as immunofluorescence assay and immunoblotting can also be readily adapted for the detection of Zika virus antibodies in a sample according to the methods of this disclosure. An ELISA method effective for the detection of the antibodies includes, for example, binding the chimeric virus or virus particles to a substrate; contacting the bound chimeric virus with a fluid or tissue sample containing the antibody; contacting the above with a secondary antibody, which is reactive with the bound antibody, bound to a detectable moiety (for example, horseradish peroxidase enzyme or alkaline phosphatase enzyme); contacting the above with the substrate for the enzyme; contacting the above with a color reagent; and observing/measuring color change or development.

The immune response following a flavivirus infection includes the production of IgM and IgG antibodies, which are primarily directed against the flavivirus E protein. IgM antibody capture (MAC) or IgG antibody capture (GAC) ELISAs are commonly used to detect the level of IgM or IgG (respectively) in serum samples of patients suspected of having a flavivirus (such as a Zika virus) infection. In these assays, anti-human IgM or anti-human IgG serves as a capture antibody and is coated onto an appropriate assay plate, such as a multi-well plate. After blocking of the plate, such as with nonfat dry milk, diluted human sera are reacted with the anti-human IgM or IgG. In the context of the present disclosure, chimeric virus, which serves as the antigen, is added to the plates. A ZIKV antigen-specific antibody conjugated to a detectable label (for example, an enzyme or fluorophore) is then reacted with the immobilized virus. The detectable label is then measured to detect the presence of ZIKV-specific antibodies that were present in the serum sample. Serial dilutions of positive sera can be evaluated. The maximum dilution that exhibits positive signal is the titer for the serum. The titer of the MAC-ELISA or GAC-ELISA can be compared with the titers of other tests, such as hemagglutination inhibition tests (HIT) or PRNT. Serum samples can also be tested on control antigen in addition to viral antigen, to reduce the number of false-positive results due to non-specific binding of the serum or other factors (U.S. Patent Application Publication No. 2006/0115896).

Indirect ELISAs to detect the presence of virus-specific antibodies are typically carried out by coating a microtiter plate with an antigen-specific antibody (such as a flavivirus-cross reactive or ZIKV-specific antibody), blocking the plates to prevent non-specific binding to the plate surface, and adding virus antigen (such as a chimeric virus disclosed herein) to allow binding of the antigen to the virus-specific antibody. After several washes, diluted human sera is added to allow binding of any antibodies present in the sample to the immobilized viral antigens (e.g. the chimeric virus antigens). IgM or IgG antibodies that were present in the sample are then detected using a labelled secondary antibody, such as anti-human IgG or anti-human IgM conjugated to a detectable label (such as an enzyme or fluorophore). The presence of ZIKV-specific antibody is detected by measuring the detectable label (for example, by measuring fluorescence, optical density or colorimetric absorbance).

In some embodiments herein, detection of Zika virus-specific antibodies in a sample is performed by providing a chimeric virus disclosed herein bound to a solid support; contacting the chimeric virus-bound solid support with the sample under conditions sufficient to form virus-antibody complexes if Zika virus-specific antibodies are present in the sample; contacting the virus-antibody complexes with a secondary antibody; and detecting binding of the secondary antibody to the virus-antibody complexes.

In other embodiments herein, detection Zika virus-specific antibodies in a sample is carried out by providing a secondary antibody bound to a solid support; contacting the secondary antibody-bound solid support with the sample under conditions sufficient to allow binding of the secondary antibody to any Zika virus-specific antibodies present in the sample, thereby forming antibody-antibody complexes; contacting the antibody-antibody complexes with a chimeric virus disclosed herein under conditions sufficient for the chimeric virus to bind the Zika virus-specific antibodies, thereby forming immune complexes; and detecting the presence of the immune complexes, thereby detecting Zika virus-specific antibodies in the sample. In some examples, detecting the presence of the immune complexes includes contacting the immune complexes with an antibody that specifically binds the chimeric virus and comprises a detectable label.

In yet other embodiments, detection of Zika virus-specific antibodies in a sample includes the steps of providing a Zika virus-specific antibody bound to a solid support; contacting the antibody-bound solid support with a chimeric virus disclosed herein under conditions sufficient for the chimeric virus to bind the Zika virus-specific antibody to form antibody-virus complexes; contacting the antibody-virus complexes with the sample to allow binding of any Zika virus-specific antibodies present in the sample to the chimeric virus, thereby forming immune complexes; contacting the immune complexes with a secondary antibody; and detecting binding of the secondary antibody to the immune complexes, thereby detecting Zika virus-specific antibodies present in the sample.

A detectable moiety allows for visual detection of a precipitate or a color change, visual detection by microscopy (such as a chromogenic deposit or fluorescence), or automated detection by spectrometry, radiometric measurement or the like. Examples of detectable moieties include fluorescein, fluorescein isothiocyanate, rhodamine, Cy5, and Cy3 (for fluorescence microscopy and/or the microsphere-based immunoassay), horseradish peroxidase (for either light or electron microscopy and biochemical detection), biotin-streptavidin (for light or electron microscopy) and alkaline phosphatase (for biochemical detection by color change).

Another immunologic technique that can be useful in the detection of flavivirus antibodies uses mAbs for detection of antibodies specifically reactive with flavivirus polypeptides in a competitive inhibition assay. Briefly, a sample is contacted with a chimeric flavivirus or virus particle of the present disclosure which is bound to a substrate (for example, a 96-well plate). Excess sample is thoroughly washed away. A labeled (for example, enzyme-linked, fluorescent, radioactive, etc.) mAb is then contacted with any previously formed polypeptide-antibody complexes and the amount of mAb binding is measured. The amount of inhibition of mAb binding is measured relative to a control (no antibody), allowing for detection and measurement of antibody in the sample. The degree of mAb binding inhibition can be a very specific assay for detecting a particular flavivirus variety or strain, when based on mAb binding specificity for a particular variety or strain of flavivirus. mAbs can also be used for direct detection of flavivirus in cells by, for example, immunofluorescence assays according to standard methods.

As a further example, a micro-agglutination test can be used to detect the presence of Zika virus antibodies in a sample. Briefly, latex beads, red blood cells or other agglutinable particles are coated with a chimeric flavivirus or virus particles of this disclosure and mixed with a sample, such that antibodies in the sample that are specifically reactive with the antigen crosslink with the antigen, causing agglutination. The agglutinated antigen-antibody complexes form a precipitate, visible with the naked eye or measurable by spectrophotometer.

In yet another example, a microsphere-based immunoassay can be used to detect the presence of flavivirus antibodies in a sample. Microsphere immunoassays (MIAs) are becoming increasingly popular for laboratory diagnosis of many diseases (Earley et al., *Cytometry* 50:239-242, 2002; Kellar et al., *Cytometry* 45:27-36, 2001). The technology involves the detection and analysis of a reaction (such as an antibody or other ligand) attached to microspheres or beads. The detecting instrument is a simplified flow cytometer, and lasers simultaneously identify the microsphere sets and measure the fluorescence associated with the reaction. The speed at which these tests can be performed and the ability to multiplex make this methodology particularly useful.

A MIA can be used to detect the presence of Zika virus-specific antibodies in a sample. In some embodiments, microsphere beads are coated with a ZIKV-specific antibody and contacted with a chimeric virus (as disclosed herein) such that the chimeric viruses bind to the microsphere-bound Zika virus-specific antibodies. The microsphere immune complexes are mixed with a serum sample such that antibodies in the sample that are specifically reactive with the chimeric viruses bind the viruses bound (indirectly) to the microsphere. The bead-bound immune complexes are allowed to react with fluorescent-dye labeled anti-species antibody (such as PE-labeled anti-human IgM or anti-human

IgG), and are measured using a microsphere reader (such as a Luminex instrument). In an alternative embodiment, microsphere beads are coated directly with the chimeric viruses and virus-bound microspheres are contacted with the serum samples.

Lateral flow assays (LFAs) are another method by which antigen-specific antibodies (or pathogen-specific antigens) can be detected in biological samples. These assays are generally very rapid and enable point of care testing. LFA is performed over a strip, different parts of which are assembled on a plastic backing. These parts are sample application pad, conjugate pad, nitrocellulose membrane and adsorption pad. Nitrocellulose membrane is further divided into test and control lines. Pre-immobilized reagents at different parts of the strip become active upon flow of liquid sample. LFA combines the unique advantages of biorecognition probes and chromatography.

Several designs have been developed for lateral flow assays. Generally LFAs include a porous support strip (such as a strip of cellulose) with a number of separate regions spaced horizontally along the support. The solid support need not be identical in all regions of a strip. Typically, the first region is a sample pad where a biological fluid is applied to flow laterally through the support to the remaining regions. The second region generally contains a labeling moiety that can be bound to the analyte of interest (such as an antibody or protein) in the sample if present. Downstream of the labeling region is a capture or "test" region where the labeled analyte (for example, antibody or peptide) is retained in the strip. It is in this test region where detection is generally performed. In addition to the test region, the strip may contain a control region either in the same flow path as that of the test region, or in a parallel path on the strip. There may also be a reservoir downstream of the various regions to absorb the sample that has traversed the test strip.

LFAs can be direct assays, forming sandwiches in proportion to the level of analyte present, or may be competition assays where analyte in the sample diminishes the amount of label detected in the detection zone. In direct sandwich assays, for example, the sample may be labeled by colored particles that are coupled to affinity reagents such as secondary antibodies that bind ZIKV-specific antibodies present in the sample, forming complexes which are then carried to the test region for capture by an additional reagent. The detectable label in the test region will be directly proportional to the level of peptide in the sample.

In competitive assays, the labeling region may contain labeled reagents, for example, that are already coupled to the target analyte (e.g. antibody) or an analog thereof, and the analytes in the sample compete with this labeled material for capture by the capture reagent in the test region. In this case, the detectable label in the test region will be inversely proportional to the quantity of analyte in the sample itself.

Simple visual detection is the most common means of reading an LFA, however, there are commercially available lateral flow readers that can quantitate the detectable label in the test region.

LFAs can be used, for example, to detect antigen-specific antibodies present in a biological sample (such as a serum sample) that specifically recognize ZIKV.

VII. Peripheral Challenge Model and Evaluation of Candidate Vaccine Efficacy

The chimeric viruses disclosed herein can also be used in the development of a peripheral challenge mouse model for ZIKV vaccine evaluation. It has been shown that mouse models established for ZIKV infection have limitations. In particular, many strains of mice are not susceptible to most wt ZIKV challenge by peripheral injection routes. Since the chimeric WN/ZKV disclosed herein are based on the WNV genetic backbone that is highly infective in many strains of mouse at any age, the chimeric viruses could be used as challenge viruses that are virulent in some of the mouse strain that are resistant to wt ZIKV infection.

Thus, the chimeric flaviviruses disclosed herein may be used in methods to assess the efficacy of candidate vaccines, such as ZIKV vaccine candidates. In some examples, the efficacy of candidate ZIKV vaccines are tested by inoculating subjects (for example, mice or non-human primates (such as rhesus monkeys)) with a candidate vaccine, followed by challenge with a virulent ZIKV strain. The disclosed WN/ZKV chimeras are virulent and/or generate significant viremia in non-immunized mice, therefore they can be used as the challenge dose in previously inoculated subjects.

In one particular embodiment, a set of subjects (such as mice) is inoculated with a candidate ZIKV vaccine. Administration of the candidate vaccine strain virus may be carried out by any suitable means, including by parenteral injection (such as intraperitoneal, subcutaneous, or intramuscular injection). In a particular example, the subjects are inoculated intraperitoneally with candidate vaccine virus in a vehicle such as phosphate buffered saline. Multiple inoculations (such as boosters) may be carried out, separated by a suitable period of time, such as at least two weeks, four weeks, eight weeks, twelve weeks, or more.

Subjects that have been test vaccinated with the candidate vaccine are challenged with a virulent or lethal dose of a WN/ZKV chimera disclosed herein following a suitable period of time to allow immunity based on the vaccination to develop (such as at least two weeks, four weeks, eight weeks, twelve weeks, or more). The challenge dose is administered by any suitable route including those above, and optionally is administered by the same or a different route as the vaccinating dose. Following the challenge dose, subjects are monitored for development of morbidity (such as fever, rash, vomiting, loss of appetite, rough fur, hunched back, lethargy, unbalanced or irritable movement, dehydration, weight loss, or signs of paralysis) or mortality. In addition, blood is collected from subjects after challenge for measurement of viremia levels. A decrease in viremia levels, signs of morbidity and/or mortality compared to a set of control subjects which is not inoculated with the candidate vaccine (for example, a decrease of at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% in a test vaccinated population compared with a control population) indicates the effectiveness of the candidate vaccine.

The following examples are provided to illustrate certain particular features and/or embodiments. These examples should not be construed to limit the disclosure to the particular features or embodiments described.

EXAMPLES

Example 1: Construction of Chimeric West Nile/Zika Viruses

This example describes the construction of chimeric West Nile/Zika viruses (WN/ZKVs) that include the prM and E genes from Zika virus in a WNV backbone.

Engineering and Deriving Chimeric WN/ZKVs

Using previously engineered infectious clones of WNV (Kinney et al., *J Gen Virol* 87: 3611-3622, 2006), several chimeric WN/ZKVs that contain the prM and E genes of a Zika virus (ZIKV) in the genomic background of the WNV NY99 virus were engineered. The chimeric WN/ZKV expresses the entire ZIKV viral envelope on the virion surface, and can be used as a surrogate for ZIKV for multiple applications.

Flaviviruses encode a signal sequence (SS) at the C-terminal end of the capsid protein that serves as a signal peptide for prM during protein processing. The junction site of the chimeric constructs within the SS requires empirical investigation to obtain the most viable and stable chimeric virus. The amino acid (AA) sequences of the SS between WNV and ZIKV are not highly conserved, but both are 18 AA in length (FIG. 1). Based in part on knowledge obtained from the previous construction of various chimeric flaviviruses (U.S. Pat. No. 8,715,689 and PCT Publication No. WO 2015/196094, which are herein incorporated by reference in their entirety), three junction strategies were designed for the chimeric constructs (FIG. 1). The Z3 chimeric construct contains 15 AA of the SS from WNV and 3 AA of the SS from ZIKV; the Z5 construct contains 13 AA of the SS from WNV and 5AA from ZIKV; and the Z15 construct contain 3 AA of the SS from WNV and 15 AA from ZIKV.

All three chimeric viruses were successfully recovered from C6/36 cells transfected with chimeric viral RNA which was in vitro transcribed from engineered chimeric cDNA. Virus seeds were designated as C6/36-0 seeds when recovered from transfected C6/36 cells, and were amplified one more time in C6/36 and Vero cells to obtain the working virus seeds, C6/36-1 and C6/36-0/Vero-1, for further characterization.

Genome Sequencing of Chimeric WN/ZKVs

Initial chimeric constructs (WN/ZKV-3SPH, WN/ZKV-5SPH, and WN/ZKV-15SPH) were made using the prM-E gene sequence of the ZIKV SPH2015 strain obtained from Genbank (Accession No. KU321639.1), prior to when the PRVABC59 and R103451 strains were isolated from travelers acquiring ZIKV infection during the 2015 outbreak by the CDC diagnostic lab at Fort Collins, Colo. The R103451 (GenBank Accession No. KX262887.1; SEQ ID NO: 13) and PRVABC59 (GenBank Access No. KU501215.1; SEQ ID NO: 15) strains were available as wild-type (wt) ZIKV controls to CDC labs, but the SPH2015 strain was not. There is only 1 amino acid residue that differs between SPH2015 and R103451/PRVABC59 within the prM-E gene region included in the WN/ZIKV chimeric constructs. The difference is at E protein amino acid position 23 (E23), with an isoleucine (Ile) in the SPH2015 strain and a valine (Val) in the PRVABC59 and R103451 strains. Although the difference from Ile to Val is quite conserved, the E23 amino acid was changed to Val in one of the Z3 chimeric constructs (WN/ZKV-3PR) to make the entire prM-E amino acid sequence identical to the R103451 and PRVABC59 strains that will be used as wt ZIKV controls. For the nucleotide sequences of the prM-E, there is one nucleotide that differs (silent) between the chimeras and strain R103251, and six silent differences between the chimeras and the PRVABC59 strain. Except for the 5' and 3' 24-base termini of the viral genome, the genomes of the chimeric virus working seeds have been sequenced, and it has been verified that all of the seeds contain the correct recombinant genome sequences. The following constructs have been sequenced:

WN/ZKV-3PR (SEQ ID NOs: 1 and 2)—contains 15 AA of the SS from WNV and 3 AA of the SS from ZIKV; the nucleotide and amino sequences of this construct were modified to substitute Ile for Val at position 23 of the E protein (E23; residue 314 of SEQ ID NO: 2) to correspond to the sequence of strain PRVABC59 and R103451.

WN/ZKV-3SPH (SEQ ID NOs: 3 and 4)—contains 15 AA of the SS from WNV and 3 AA of the SS from ZIKV; includes Ile at position E23 (residue 314 of SEQ ID NO: 4), which corresponds to strain SPH2015.

WN/ZKV-5SPH (SEQ ID NOs: 5 and 6)—contains 13 AA of the SS from WNV and 5 AA of the SS from ZIKV; includes Ile at position E23 (residue 314 of SEQ ID NO: 6), which corresponds to strain SPH2015.

WN/ZKV-15SPH (SEQ ID NOs: 7 and 8)—contains 3 AA of the SS from WNV and 15 AA of the SS from ZIKV; includes Ile at position E23 (residue 314 of SEQ ID NO: 8), which corresponds to strain SPH2015.

Chimeric Virus Growth in Cells

All three types of chimeric constructs yielded viable viruses that replicated competently and reached very high titers (ranging from 10^8-10^9 pfu/ml) in C6/36 cells as early as day 3 post-infection (p.i.). In C6/36 cell cultures, rapid replication to high titer permitted the chimeric viruses to be harvested daily from day 3 to day 14. In Vero cells, the chimeric viruses caused significant cytopathic effect (CPE) starting at day 3, but still achieved high virus titers ($10'$-10^8 pfu/ml) that could be harvested daily from day 2 to day 10 p.i. All three types of chimeric constructs demonstrated similar infectivity and replication efficiency in cell cultures.

When comparing plaque size of chimeric WN/ZKV with its wt ZIKV, the chimeric plaques were significantly larger and more uniform than wt ZIKV plaques. Plaques of chimeric WN/ZKV could be clearly counted on day 3 p.i., while wt ZIKV R103451 plaques could not be readily counted until day 5-6 p.i.

PRNT Titers of Human Serum Against Chimeric WN/ZKV

In view of the faster replication rate of chimeric WN/ZKV compared to wt ZIKV, the chimeric viruses were evaluated as a ZIKV surrogate for the development of faster neutralization assays. Wild type ZIKV and chimeric WN/ZKV-3SPH were compared in the traditional plaque reduction neutralization test (PRNT). The results confirmed that chimeric WN/ZKV expressed authentic ZIKV neutralization epitopes that resulted in neutralization assay results that were equivalent to the neutralization assay using wt ZIKV (Table 3). The chimeric virus can speed up the traditional PRNT from 5-6 days to 3-4 days.

TABLE 3

Similar PRNT (90% virus reduction) titers of 13 human serum samples against chimeric WN/ZKV-3SPH virus and wt ZIKV PRVABC59

	PRNT90	
Serum ID	wt ZIKV (PRVABC59)	WN/ZKV
1	5120	5120
2	10	20
3	2560	2560
4	320	640
5	10,240	10240
6	40	80
7	2560	2560
8	640	1280
9	<10	<10
10	<10	<10
13	160	640
14	160	320
15	320	640

Live Chimeric Reporter Viruses

A fluorescent reporter gene (ZsGreen) was inserted into the chimeric WN/ZKV virus construct to generate live chimeric WN/ZKV reporter viruses. Reporter viruses were successfully generated for WN/ZKV-3SPH by insertion of the ZsGreen linked with P2A using strategy 1 (FIG. **2**, Type I reporter construct). The nucleotide and amino acid sequences of two reporter viruses (WN/ZKV-ZsG0 and WN/ZKV-ZsG1) are set forth herein as SEQ ID NOs: 9-12. The nucleotide sequence of the ZsGreen in WN/ZKV-ZsG1 (SEQ ID NO: 11) is codon-optimized for expression in human cells. The first 35 amino acid codons of the C gene immediately after ZsGreen-P2A in both chimeric constructs were edited (not human codon optimized) to make multiple silent mutations in order to minimize homologous recombination potential with the partial C35 gene upstream of ZsGreen. The C sequence was edited instead of human codon optimized because the codon optimization could result in more homologous recombination potential with the human optimized ZsGreen gene. Decreasing homologous recombination potential is expected to enhance the genetic stability of the reporter viruses. An alternative reporter virus strategy is shown in FIG. **2** (see Type II reporter construct).

Genetic Stability

Chimeric viruses are passaged serially in Vero cell cultures to determine their genetic stability. The chimeric virus exhibiting the greatest genetic stability are chosen for applications that require serial cell passages during virus production (for example, production of inactivated vaccine).

Example 2: Characterization of Chimeric WN/ZKV and R-WN/ZKV Constructs

This example describes the generation and characterization of an additional WN/ZKV reporter virus (R-WN/ZKV).

Stability of WN/ZKV and R-WN/ZKV Constructs

Example 1 describes the successful recovery of chimeric WN/ZKVs using all three of the strategies illustrated in FIG. **1**. All three types of chimeric viruses replicated efficiently in both Vero and C6/36 cells and, based on their similar plaque phenotypes in Vero cells between 1 to 10 serial passages, all three chimeric constructs appeared to be similarly stable in Vero cells. The chimeric WN/ZKV-Z3 constructs WN/ZKV-3SPH and WN/ZKV-3PR were genome sequenced after serial passages in Vero cells. Both chimeric viral genomes were quite stable after serial passage. The WN/ZKV-3SPH acquired 3 amino acid (AA) mutations, and WN/ZKV-3PR acquired only 2 AA mutations after the 10 passages.

The reporter chimeric virus constructs disclosed herein are based on WN/ZKV-3SPH or WN/ZKV-3PR. First, two reporter viruses (WN/ZKV-ZsG0 and WN/ZKV-ZsG1) based on WN/ZKV-3SPH were recovered. After genome sequencing both reporter chimeras recovered from transfection and 1 more passage in C6/36 cells, WN/ZKV-ZsG0 was found to have the expected sequence, including the full ZsGreen gene, while a small portion of the WN/ZKV-ZsG1 reporter seed lost the ZsGreen gene. After RT-PCR analysis, it was estimated that about 10% of the WN/ZKV-ZsG1 suffered deletion of the ZsGreen gene. Therefore, the WN/ZKV-ZsG0 construct was used to make the reporter chimera R-WN/ZKV-PR (based on WN/ZKV-3PR).

Similar to WN/ZKV-ZsG0, R-WN/ZKV-PR was constructed with the type 1 reporter construct shown in FIG. **2**. The reporter genome contains WNV 5'NCR, WNV partial C gene (first 35 AA with wt sequence), ZsGreen gene (wt) linked with a self-cleavage 2A peptide from porcine teschovirus-1 (P2A), a full WNV C gene with its first 35 AA codon edited, the first 15 AA of the WNV prM signal sequence and the last 3 AA of the ZIKV prM signal sequence, the prM and E genes of ZIKV, and all of the NS genes and the 3'NCR of WNV (FIG. **3**). The nucleotide and amino acid sequences of R-WN/ZKV-PR are set forth herein as SEQ ID NO: 19 and SEQ ID NO: 20, respectively. Serial passaging of R-WN/ZKV-PR indicated that the ZsG0 gene in the construct was stable up to 4 passages in Vero cells and 5 passages in C6/36 cells (FIG. **4**). Therefore, it was determined that the working stock of the reporter virus should be limited to low cell passage levels, less than a total of three passages after deriving the virus from transfection of the in vitro transcribed recombinant viral RNA (FIG. **5**).

In addition, every reporter virus lot generated is confirmed for ZsGreen gene stability and expression by dual-fluorescent flow cytometry analysis. Cells infected with pre-master seed (PMS), master seed (MS), or working stock (WS) of the R-WN/ZKV-PR were immunostained with a rabbit monoclonal WNV capsid Ab followed by a goat anti-rabbit Ab conjugated with Alexa Fluor 647 (AF647) fluorophore after 24-48 hours of infection. Flow cytometry results in FIG. **5** show an example in which 98% of infected cells co-expressed both WNV C protein (AF647) and ZsG0 protein (ZsGreen), while only 0.1% of cells showed low positivity to WNV C protein only, and only 1.4% of cells showed positivity to ZsG0 only. Using RT-PCR and flow cytometry, the PMS, MS, and WS lots of R-WN/ZKV-PR were analyzed, and all three lots had an intact ZsG0 gene and showed a high level of co-expression of WNV C and ZsG0 proteins in the infected cells. These two assays serve as quality control assays for each lot of reporter virus generated.

Chimeric WN/ZKV and WN/DENVs for Fast and Synchronized PRNT and mFRNT to ZIKV and DENVs

The WNV NY99 strain replicates significantly faster than wt DENV and ZIKV in multiple cell cultures, including Vero, LLC-MK2, and BHK-21 cells that are widely used for cell based neutralization antibody assays. Unlike ELISA that measures all types of antibodies, the neutralization test measures antibodies capable of neutralizing the viruses. Because it is more specific than ELISA, the neutralization test has been used as a confirmative serological assay after positive results of ELISA in diagnosis.

Upon binding to viruses, the neutralization antibodies (Nt Abs) block virus infection of cells (mostly during virus entry stage) and are the most important B cell immune response product in directly fighting many viral infections. Therefore, the neutralization test is also one of the most important functional immunological assays in analyses of vaccine efficacy. However, most of the cell-based neutralization tests are time-consuming and labor-intensive. The traditional gold-standard plaque-reduction neutralization test (PRNT) used in detecting Nt Abs to many flaviviruses typically has used 6- to 24-well plates, and required multiple days of cell infection before the virus plaques formed on the infected cell sheet under an agarose medium overlay can be stained and become visible for counting. The faster micro-focus neutralization test (mFRNT) typically uses 96-well micro plates, and the viral micro-foci can be detected and counted by microplate reader (such as ELISPOT reader or image-based cytometry reader) after immunostaining by viral Abs of the cell sheet within 1-2 days post infection.

Because ZIKV and DENVs are transmitted by the same mosquito vectors, *Ae. aegypti* and *Ae. albopictus*, most recent ZIKV outbreaks happen in areas that are also endemic for DENVs. Due to significant cross-reactivity of flavivirus antibodies, it is very difficult to differentiate infection among

ZIKV and the four types of DENV in secondary ZIKV- or DENV-infected cases. For example, during confirmative diagnosis by PRNT for recent ZIKV outbreaks, it is necessary to conduct a PRNT assay against ZIKV and multiple types (typically at least 2) of DENV for the same clinical samples. Because DENVs and ZIKV have different replication rates in Vero cells, the duration of PRNT for each virus is different. Such differential testing schedule complicates the streaming of diagnostic effort. By using chimeric WN/DENVs and WN/ZKV for the PRNT, it is possible to synchronize the assay duration to three days post infection (pi). As indicated in the Table 4, wt DENVs require 6 to 9 days, depending on the DENV strain, to produce visible plaques, while the wt ZIKV takes at least 5 days p.i. to show countable plaques. On the other hand, all chimeric WN/DENVs and WN/ZKV produced clear plaques by 3 days p.i. Therefore, using the chimeric viruses, it was possible to decrease the PRNT duration by approximately 50% and obtain results for all viruses on the same day. A panel of human serum specimens were tested to confirm that use of the chimeric WN/DENVs and WN/ZIKV resulted in similar PRNT titers as those that were obtained when using wt DENVs and wt ZIKV (Table 3 shows WN/ZKV vs ZIKV results).

TABLE 4

Chimeric viruses form plaques faster than wt parental viruses in Vero cells Visible Plaques (day p.i.)

WNV	3		
DENV-1	6-8	WN/DENV-1	3
DENV-2	7-9	WN/DENV-2	3
DENV-3	6-8	WN/DENV-3	3
DENV-4	6-8	WN/DENV-4	3
ZIKV	5-7	WN/ZIKV	3

R-WN/ZKV-PR for Fast, Easy, and High-Throughput Fluoro-mFRNT or Cell Infection Rate Reduction Assay

Although much faster and higher throughput than the PRNT, the typical mFRNT is still labor intensive. The procedures include adding and removing the carboxyl methyl cellulose overlays from cell plates, cell fixation, and multiple immunostaining procedures. R-WN/ZKV-PR was used to largely simplify and optimize the mFRNT to a fluoro-mFRNT that can be live-imaged by an image-based cytometry plate reader to detect the fluorescent viral foci on infected cell sheets. Due to the fast replication efficiency of the WN/ZKV and strong ZsG0 reporter signal, the infected cells can be measured within 24 hours p.i. With a live-imaging capable cytometry plate reader, it was possible to directly read the infected 96-well plate without any CMC overly, cell fixation, or immunostaining process. FIG. **6** shows a comparison of the PRNT, mFRNT, and fluoro-mFRNT procedures.

A small panel of human serum specimens were tested with the fluoro-mFRNT using R-WN/ZKV-PR. The neutralizing Ab titer results were very comparable to the traditional gold-standard PRNT using wt ZIKV (Table 5). In addition to the fluoro-mFRNT, R-WN/ZKV-PR can also be used in other cytometry-based neutralization assays, which measure reduction of the percent cell infection rate instead of the reduction in viral foci formation. The same image-cytometry plate reader was used to evaluate such an assay with R-WN/ZKV-PR, and the results indicated that a wide linear range of the cell infection rate can be easily achieved by R-WN/ZKV-PR, suggesting its utility for the percent cell infection reduction-based Nt assay.

TABLE 5

Comparable results between PRNT using wt ZIKV and Fluoro-mFRNT using R-WN/ZKV

Serum ID	wt ZIKV PRNT90*	R-WN/ZKV F-mFRNT90*
20	1280	640/1280
21	10240	2560/5120
22	2560	1280
23	5120	1280/2860
30	160	320/640
32	2560	1280
33	20480	10240/20480
38	640	640/1280
39	1280	2560
44	320	640

*At least 90% reduction

Mouse Challenge Study

WN/ZKV-3PR was tested in CD-1 and AG129 mice. The results showed that the CD-1 immune competent, outbred mice were not susceptible to WN/ZKV-3PR or wt ZIKV, but were highly susceptible to wt WNV (Table 6). In the interferon-α, -β, -γ receptor knockout AG129 mice, WN/ZKV was also attenuated relative to WNV, but caused a mortality rate similar to or somewhat higher than that of wt ZIKV (Table 7). AG129 mice infected with WN/ZKV had significantly shorter survival time than wt ZIKV-infected AG129. Overall, the results showed that WN/ZKV was more similar to the BSL-2 wt ZIKV in mice than the BSL-3 WNV. Therefore, these results support laboratory containment at BSL-2 when working with chimeric WN/ZKV.

TABLE 6

Three week-old CD-1 mice by intra-peritoneal challenge

Virus/dose (pfu)	Survival	AST* ± SD
ZIKV PRVABC59/10^6	100%	NA
WN/ZIKV-3PR/10^6	100%	NA
WN/ZIKV-3PR/10^5	100%	NA
WN/ZIKV-3PR/10^4	100%	NA
WN/ZIKV-3PR/10^3	100%	NA
WN NY99/10^3	0%	8 ± 0

*AST = Average Survival Time

TABLE 7

AG129 mice (≥20 week-old) by intraperitoneal challenge

Virus/dose (pfu)	Survival	AST* ± SD
ZIKV PRVABC59/10^4	0%	13.6 ± 1.2
ZIKV PRVABC59/10^3	0%	18.6 ± 3.5
ZIKV PRVABC59/10^2	40%	19.7 ± 1.89
WN/ZIKV-3PR/10^3	0%	5.2 ± 0.4
WN/ZIKV-3PR/10^2	20%	6 ± 0
WN/ZIKV-3PR/10	40%	7.3 ± 2.6
WN NY99/10^2	0%	3.1 ± 0.4
WN NY99/10	20%	3.8 ± 0.4

*AST = Average Survival Time

Mosquito Study

A mosquito infection experiment was initiated with the chimeric viruses WN/ZKV-3PR and R-WN/ZKV-PR. Results from a small number of infected mosquitoes have shown an absence of infectivity or very low infectivity of the chimeric viruses for the Culex mosquito vector of WNV. To further reduce the potential for infection of mosquitos, miRNAs specific to mosquito cells are incorporated into

WN/ZKV and R-WN/ZKV to evaluate whether such miRNA can be used to eliminate any potential of mosquito transmission of the virus. Specifically, miRNA-14, miRNA-184, and miRNA-1175 are investigated.

In view of the many possible embodiments to which the principles of the disclosed invention may be applied, it should be recognized that the illustrated embodiments are only preferred examples of the invention and should not be taken as limiting the scope of the invention. Rather, the scope of the invention is defined by the following claims. We therefore claim as our invention all that comes within the scope and spirit of these claims.

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cacaaagttg tgaaagtgat gcgcccggct gctgatggaa gaaccgtcat ggatgttatc   9480

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ctgcggctca tggccaacgc catttgctcc gctgtccctg tgaattgggt ccctaccgga  10080

agaaccacgt ggtccatcca tgcaggagga gagtggatga caacagagga catgttggag  10140

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t                                                                  11041
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<211> LENGTH: 3437
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 2

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Ala Met Leu Ser Leu Ile Asp Gly Lys Gly Pro Ile Arg Phe Val Leu
        35                  40                  45

Ala Leu Leu Ala Phe Phe Arg Phe Thr Ala Ile Ala Pro Thr Arg Ala
    50                  55                  60

Val Leu Asp Arg Trp Arg Gly Val Asn Lys Gln Thr Ala Met Lys His
65                  70                  75                  80

Leu Leu Ser Phe Lys Lys Glu Leu Gly Thr Leu Thr Ser Ala Ile Asn
                85                  90                  95

Arg Arg Ser Ser Lys Gln Lys Lys Arg Gly Gly Lys Thr Gly Ile Ala
            100                 105                 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Arg Thr Leu Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly
385                 390                 395                 400
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Lys Gly Ser Leu Val Thr Cys Ala Lys Phe Ala Cys Ser Lys Lys Met
                405                 410                 415

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ile Asp Ile Ser Arg Gln Glu Leu Arg Cys Gly Ser Gly Val Phe Ile
                805                 810                 815
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```
His Asn Asp Val Glu Ala Trp Met Asp Arg Tyr Lys Tyr Tyr Pro Glu
            820                 825                 830

Thr Pro Gln Gly Leu Ala Lys Ile Ile Gln Lys Ala His Lys Glu Gly
        835                 840                 845

Val Cys Gly Leu Arg Ser Val Ser Arg Leu Glu His Gln Met Trp Glu
    850                 855                 860

Ala Val Lys Asp Glu Leu Asn Thr Leu Leu Lys Glu Asn Gly Val Asp
865                 870                 875                 880

Leu Ser Val Val Val Glu Lys Gln Glu Gly Met Tyr Lys Ser Ala Pro
                885                 890                 895

Lys Arg Leu Thr Ala Thr Thr Glu Lys Leu Glu Ile Gly Trp Lys Ala
            900                 905                 910

Trp Gly Lys Ser Ile Leu Phe Ala Pro Glu Leu Ala Asn Asn Thr Phe
        915                 920                 925

Val Val Asp Gly Pro Glu Thr Lys Glu Cys Pro Thr Gln Asn Arg Ala
    930                 935                 940

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

Arg Met Phe Leu Lys Val Arg Glu Ser Asn Thr Thr Glu Cys Asp Ser
                965                 970                 975

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

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

Arg Ala  Val Leu Gly Glu Val  Lys Ser Cys Thr Trp  Pro Glu Thr
    1010                1015                1020

His Thr  Leu Trp Gly Asp Gly  Ile Leu Glu Ser Asp  Leu Ile Ile
    1025                1030                1035

Pro Val  Thr Leu Ala Gly Pro  Arg Ser Asn His Asn  Arg Arg Pro
    1040                1045                1050

Gly Tyr  Lys Thr Gln Asn Gln  Gly Pro Trp Asp Glu  Gly Arg Val
    1055                1060                1065

Glu Ile  Asp Phe Asp Tyr Cys  Pro Gly Thr Thr Val  Thr Leu Ser
    1070                1075                1080

Glu Ser  Cys Gly His Arg Gly  Pro Ala Thr Arg Thr  Thr Thr Glu
    1085                1090                1095

Ser Gly  Lys Leu Ile Thr Asp  Trp Cys Cys Arg Ser  Cys Thr Leu
    1100                1105                1110

Pro Pro  Leu Arg Tyr Gln Thr  Asp Ser Gly Cys Trp  Tyr Gly Met
    1115                1120                1125

Glu Ile  Arg Pro Gln Arg His  Asp Glu Lys Thr Leu  Val Gln Ser
    1130                1135                1140

Gln Val  Asn Ala Tyr Asn Ala  Asp Met Ile Asp Pro  Phe Gln Leu
    1145                1150                1155

Gly Leu  Leu Val Val Phe Leu  Ala Thr Gln Glu Val  Leu Arg Lys
    1160                1165                1170

Arg Trp  Thr Ala Lys Ile Ser  Met Pro Ala Ile Leu  Ile Ala Leu
    1175                1180                1185

Leu Val  Leu Val Phe Gly Gly  Ile Thr Tyr Thr Asp  Val Leu Arg
    1190                1195                1200

Tyr Val  Ile Leu Val Gly Ala  Ala Phe Ala Glu Ser  Asn Ser Gly
    1205                1210                1215

Gly Asp  Val Val His Leu Ala  Leu Met Ala Thr Phe  Lys Ile Gln
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    1220                1225                1230

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

Gln Glu  Asn Ile Leu Leu Met  Leu Ala Ala Val Phe  Phe Gln Met
    1250                1255                1260

Ala Tyr  Tyr Asp Ala Arg Gln  Ile Leu Leu Trp Glu  Ile Pro Asp
    1265                1270                1275

Val Leu  Asn Ser Leu Ala Val  Ala Trp Met Ile Leu  Arg Ala Ile
    1280                1285                1290

Thr Phe  Thr Thr Thr Ser Asn  Val Val Val Pro Leu  Leu Ala Leu
    1295                1300                1305

Leu Thr  Pro Gly Leu Arg Cys  Leu Asn Leu Asp Val  Tyr Arg Ile
    1310                1315                1320

Leu Leu  Leu Met Val Gly Ile  Gly Ser Leu Ile Arg  Glu Lys Arg
    1325                1330                1335

Ser Ala  Ala Ala Lys Lys Lys  Gly Ala Ser Leu Leu  Cys Leu Ala
    1340                1345                1350

Leu Ala  Ser Thr Gly Leu Phe  Asn Pro Met Ile Leu  Ala Ala Gly
    1355                1360                1365

Leu Ile  Ala Cys Asp Pro Asn  Arg Lys Arg Gly Trp  Pro Ala Thr
    1370                1375                1380

Glu Val  Met Thr Ala Val Gly  Leu Met Phe Ala Ile  Val Gly Gly
    1385                1390                1395

Leu Ala  Glu Leu Asp Ile Asp  Ser Met Ala Ile Pro  Met Thr Ile
    1400                1405                1410

Ala Gly  Leu Met Phe Ala Ala  Phe Val Ile Ser Gly  Lys Ser Thr
    1415                1420                1425

Asp Met  Trp Ile Glu Arg Thr  Ala Asp Ile Ser Trp  Glu Ser Asp
    1430                1435                1440

Ala Glu  Ile Thr Gly Ser Ser  Glu Arg Val Asp Val  Arg Leu Asp
    1445                1450                1455

Asp Asp  Gly Asn Phe Gln Leu  Met Asn Asp Pro Gly  Ala Pro Trp
    1460                1465                1470

Lys Ile  Trp Met Leu Arg Met  Val Cys Leu Ala Ile  Ser Ala Tyr
    1475                1480                1485

Thr Pro  Trp Ala Ile Leu Pro  Ser Val Val Gly Phe  Trp Ile Thr
    1490                1495                1500

Leu Gln  Tyr Thr Lys Arg Gly  Gly Val Leu Trp Asp  Thr Pro Ser
    1505                1510                1515

Pro Lys  Glu Tyr Lys Lys Gly  Asp Thr Thr Thr Gly  Val Tyr Arg
    1520                1525                1530

Ile Met  Thr Arg Gly Leu Leu  Gly Ser Tyr Gln Ala  Gly Ala Gly
    1535                1540                1545

Val Met  Val Glu Gly Val Phe  His Thr Leu Trp His  Thr Thr Lys
    1550                1555                1560

Gly Ala  Ala Leu Met Ser Gly  Glu Gly Arg Leu Asp  Pro Tyr Trp
    1565                1570                1575

Gly Ser  Val Lys Glu Asp Arg  Leu Cys Tyr Gly Gly  Pro Trp Lys
    1580                1585                1590

Leu Gln  His Lys Trp Asn Gly  Gln Asp Glu Val Gln  Met Ile Val
    1595                1600                1605

Val Glu  Pro Gly Arg Asn Val  Lys Asn Val Gln Thr  Lys Pro Gly
    1610                1615                1620
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Val Phe  Lys Thr Pro Glu Gly  Glu Ile Gly Ala Val  Thr Leu Asp
    1625                 1630                 1635

Phe Pro  Thr Gly Thr Ser Gly  Ser Pro Ile Val Asp  Lys Asn Gly
    1640                 1645                 1650

Asp Val  Ile Gly Leu Tyr Gly  Asn Gly Val Ile Met  Pro Asn Gly
    1655                 1660                 1665

Ser Tyr  Ile Ser Ala Ile Val  Gln Gly Glu Arg Met  Asp Glu Pro
    1670                 1675                 1680

Ile Pro  Ala Gly Phe Glu Pro  Glu Met Leu Arg Lys  Lys Gln Ile
    1685                 1690                 1695

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

Leu Pro  Gln Ile Ile Lys Glu  Ala Ile Asn Arg Arg  Leu Arg Thr
    1715                 1720                 1725

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

Ala Leu  Arg Gly Leu Pro Ile  Arg Tyr Gln Thr Ser  Ala Val Pro
    1745                 1750                 1755

Arg Glu  His Asn Gly Asn Glu  Ile Val Asp Val Met  Cys His Ala
    1760                 1765                 1770

Thr Leu  Thr His Arg Leu Met  Ser Pro His Arg Val  Pro Asn Tyr
    1775                 1780                 1785

Asn Leu  Phe Val Met Asp Glu  Ala His Phe Thr Asp  Pro Ala Ser
    1790                 1795                 1800

Ile Ala  Ala Arg Gly Tyr Ile  Ser Thr Lys Val Glu  Leu Gly Glu
    1805                 1810                 1815

Ala Ala  Ala Ile Phe Met Thr  Ala Thr Pro Pro Gly  Thr Ser Asp
    1820                 1825                 1830

Pro Phe  Pro Glu Ser Asn Ser  Pro Ile Ser Asp Leu  Gln Thr Glu
    1835                 1840                 1845

Ile Pro  Asp Arg Ala Trp Asn  Ser Gly Tyr Glu Trp  Ile Thr Glu
    1850                 1855                 1860

Tyr Thr  Gly Lys Thr Val Trp  Phe Val Pro Ser Val  Lys Met Gly
    1865                 1870                 1875

Asn Glu  Ile Ala Leu Cys Leu  Gln Arg Ala Gly Lys  Lys Val Val
    1880                 1885                 1890

Gln Leu  Asn Arg Lys Ser Tyr  Glu Thr Glu Tyr Pro  Lys Cys Lys
    1895                 1900                 1905

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

Gly Ala  Asn Phe Lys Ala Ser  Arg Val Ile Asp Ser  Arg Lys Ser
    1925                 1930                 1935

Val Lys  Pro Thr Ile Ile Thr  Glu Gly Glu Gly Arg  Val Ile Leu
    1940                 1945                 1950

Gly Glu  Pro Ser Ala Val Thr  Ala Ala Ser Ala Ala  Gln Arg Arg
    1955                 1960                 1965

Gly Arg  Ile Gly Arg Asn Pro  Ser Gln Val Gly Asp  Glu Tyr Cys
    1970                 1975                 1980

Tyr Gly  Gly His Thr Asn Glu  Asp Asp Ser Asn Phe  Ala His Trp
    1985                 1990                 1995

Thr Glu  Ala Arg Ile Met Leu  Asp Asn Ile Asn Met  Pro Asn Gly
    2000                 2005                 2010
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Leu Ile  Ala Gln Phe Tyr Gln  Pro Glu Arg Glu Lys  Val Tyr Thr
    2015                 2020                 2025

Met Asp  Gly Glu Tyr Arg Leu  Arg Gly Glu Glu Arg  Lys Asn Phe
    2030                 2035                 2040

Leu Glu  Leu Leu Arg Thr Ala  Asp Leu Pro Val Trp  Leu Ala Tyr
    2045                 2050                 2055

Lys Val  Ala Ala Ala Gly Val  Ser Tyr His Asp Arg  Arg Trp Cys
    2060                 2065                 2070

Phe Asp  Gly Pro Arg Thr Asn  Thr Ile Leu Glu Asp  Asn Asn Glu
    2075                 2080                 2085

Val Glu  Val Ile Thr Lys Leu  Gly Glu Arg Lys Ile  Leu Arg Pro
    2090                 2095                 2100

Arg Trp  Ile Asp Ala Arg Val  Tyr Ser Asp His Gln  Ala Leu Lys
    2105                 2110                 2115

Ala Phe  Lys Asp Phe Ala Ser  Gly Lys Arg Ser Gln  Ile Gly Leu
    2120                 2125                 2130

Ile Glu  Val Leu Gly Lys Met  Pro Glu His Phe Met  Gly Lys Thr
    2135                 2140                 2145

Trp Glu  Ala Leu Asp Thr Met  Tyr Val Val Ala Thr  Ala Glu Lys
    2150                 2155                 2160

Gly Gly  Arg Ala His Arg Met  Ala Leu Glu Glu Leu  Pro Asp Ala
    2165                 2170                 2175

Leu Gln  Thr Ile Ala Leu Ile  Ala Leu Leu Ser Val  Met Thr Met
    2180                 2185                 2190

Gly Val  Phe Phe Leu Leu Met  Gln Arg Lys Gly Ile  Gly Lys Ile
    2195                 2200                 2205

Gly Leu  Gly Gly Ala Val Leu  Gly Val Ala Thr Phe  Phe Cys Trp
    2210                 2215                 2220

Met Ala  Glu Val Pro Gly Thr  Lys Ile Ala Gly Met  Leu Leu Leu
    2225                 2230                 2235

Ser Leu  Leu Leu Met Ile Val  Leu Ile Pro Glu Pro  Glu Lys Gln
    2240                 2245                 2250

Arg Ser  Gln Thr Asp Asn Gln  Leu Ala Val Phe Leu  Ile Cys Val
    2255                 2260                 2265

Met Thr  Leu Val Ser Ala Val  Ala Ala Asn Glu Met  Gly Trp Leu
    2270                 2275                 2280

Asp Lys  Thr Lys Ser Asp Ile  Ser Ser Leu Phe Gly  Gln Arg Ile
    2285                 2290                 2295

Glu Val  Lys Glu Asn Phe Ser  Met Gly Glu Phe Leu  Leu Asp Leu
    2300                 2305                 2310

Arg Pro  Ala Thr Ala Trp Ser  Leu Tyr Ala Val Thr  Thr Ala Val
    2315                 2320                 2325

Leu Thr  Pro Leu Leu Lys His  Leu Ile Thr Ser Asp  Tyr Ile Asn
    2330                 2335                 2340

Thr Ser  Leu Thr Ser Ile Asn  Val Gln Ala Ser Ala  Leu Phe Thr
    2345                 2350                 2355

Leu Ala  Arg Gly Phe Pro Phe  Val Asp Val Gly Val  Ser Ala Leu
    2360                 2365                 2370

Leu Leu  Ala Ala Gly Cys Trp  Gly Gln Val Thr Leu  Thr Val Thr
    2375                 2380                 2385

Val Thr  Ala Ala Thr Leu Leu  Phe Cys His Tyr Ala  Tyr Met Val
    2390                 2395                 2400

Pro Gly  Trp Gln Ala Glu Ala  Met Arg Ser Ala Gln  Arg Arg Thr
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    2405                2410                2415

Ala Ala  Gly Ile Met Lys Asn  Ala Val Val Asp Gly  Ile Val Ala
    2420                2425                2430

Thr Asp  Val Pro Glu Leu Glu  Arg Thr Thr Pro Ile  Met Gln Lys
    2435                2440                2445

Lys Val  Gly Gln Ile Met Leu  Ile Leu Val Ser Leu  Ala Ala Val
    2450                2455                2460

Val Val  Asn Pro Ser Val Lys  Thr Val Arg Glu Ala  Gly Ile Leu
    2465                2470                2475

Ile Thr  Ala Ala Ala Val Thr  Leu Trp Glu Asn Gly  Ala Ser Ser
    2480                2485                2490

Val Trp  Asn Ala Thr Thr Ala  Ile Gly Leu Cys His  Ile Met Arg
    2495                2500                2505

Gly Gly  Trp Leu Ser Cys Leu  Ser Ile Thr Trp Thr  Leu Ile Lys
    2510                2515                2520

Asn Met  Glu Lys Pro Gly Leu  Lys Arg Gly Gly Ala  Lys Gly Arg
    2525                2530                2535

Thr Leu  Gly Glu Val Trp Lys  Glu Arg Leu Asn Gln  Met Thr Lys
    2540                2545                2550

Glu Glu  Phe Thr Arg Tyr Arg  Lys Glu Ala Ile Ile  Glu Val Asp
    2555                2560                2565

Arg Ser  Ala Ala Lys His Ala  Arg Lys Glu Gly Asn  Val Thr Gly
    2570                2575                2580

Gly His  Pro Val Ser Arg Gly  Thr Ala Lys Leu Arg  Trp Leu Val
    2585                2590                2595

Glu Arg  Arg Phe Leu Glu Pro  Val Gly Lys Val Ile  Asp Leu Gly
    2600                2605                2610

Cys Gly  Arg Gly Gly Trp Cys  Tyr Tyr Met Ala Thr  Gln Lys Arg
    2615                2620                2625

Val Gln  Glu Val Arg Gly Tyr  Thr Lys Gly Gly Pro  Gly His Glu
    2630                2635                2640

Glu Pro  Gln Leu Val Gln Ser  Tyr Gly Trp Asn Ile  Val Thr Met
    2645                2650                2655

Lys Ser  Gly Val Asp Val Phe  Tyr Arg Pro Ser Glu  Cys Cys Asp
    2660                2665                2670

Thr Leu  Leu Cys Asp Ile Gly  Glu Ser Ser Ser Ser  Ala Glu Val
    2675                2680                2685

Glu Glu  His Arg Thr Ile Arg  Val Leu Glu Met Val  Glu Asp Trp
    2690                2695                2700

Leu His  Arg Gly Pro Arg Glu  Phe Cys Val Lys Val  Leu Cys Pro
    2705                2710                2715

Tyr Met  Pro Lys Val Ile Glu  Lys Met Glu Leu Leu  Gln Arg Arg
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agccctcaga accgtctcgg aaggaggacc ccacatgttg taacttcaaa gcccaatgtc  10680

agaccacgct acggcgtgct actctgcgga gagtgcagtc tgcgatagtg ccccaggagg  10740

actgggttaa caaaggcaaa ccaacgcccc acgcggccct agccccggta atggtgttaa  10800

ccagggcgaa aggactagag gttagaggag accccgcggt ttaaagtgca cggcccagcc  10860

tggctgaagc tgtaggtcag ggaaggact agaggttagt ggagaccccg tgccacaaaa  10920

caccacaaca aaacagcata ttgacacctg ggatagacta ggagatcttc tgctctgcac  10980

aaccagccac acggcacagt gcgccgacaa tggtggctgg tggtgcgaga acacaggatc  11040

t                                                                  11041
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<210> SEQ ID NO 4
<211> LENGTH: 3437
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 4

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

Leu Lys Arg Gly Met Pro Arg Val Leu Ser Leu Ile Gly Leu Lys Arg
            20                  25                  30

Ala Met Leu Ser Leu Ile Asp Gly Lys Gly Pro Ile Arg Phe Val Leu
        35                  40                  45

Ala Leu Leu Ala Phe Phe Arg Phe Thr Ala Ile Ala Pro Thr Arg Ala
    50                  55                  60

Val Leu Asp Arg Trp Arg Gly Val Asn Lys Gln Thr Ala Met Lys His
65                  70                  75                  80

Leu Leu Ser Phe Lys Lys Glu Leu Gly Thr Leu Thr Ser Ala Ile Asn
                85                  90                  95

Arg Arg Ser Ser Lys Gln Lys Lys Arg Gly Gly Lys Thr Gly Ile Ala
            100                 105                 110

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

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

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

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

Pro Met Leu Asp Glu Gly Val Glu Pro Asp Asp Val Asp Cys Trp Cys
            180                 185                 190
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Asn Thr Thr Ser Thr Trp Val Val Tyr Gly Thr Cys His His Lys Lys
        195                 200                 205

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ile Asp Ile Ser Arg Gln Glu Leu Arg Cys Gly Ser Gly Val Phe Ile
                805                 810                 815

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

Thr Pro Gln Gly Leu Ala Lys Ile Ile Gln Lys Ala His Lys Glu Gly
        835                 840                 845

Val Cys Gly Leu Arg Ser Val Ser Arg Leu Glu His Gln Met Trp Glu
    850                 855                 860

Ala Val Lys Asp Glu Leu Asn Thr Leu Leu Lys Glu Asn Gly Val Asp
865                 870                 875                 880

Leu Ser Val Val Val Glu Lys Gln Glu Gly Met Tyr Lys Ser Ala Pro
                885                 890                 895

Lys Arg Leu Thr Ala Thr Thr Glu Lys Leu Glu Ile Gly Trp Lys Ala
            900                 905                 910

Trp Gly Lys Ser Ile Leu Phe Ala Pro Glu Leu Ala Asn Asn Thr Phe
        915                 920                 925

Val Val Asp Gly Pro Glu Thr Lys Glu Cys Pro Thr Gln Asn Arg Ala
    930                 935                 940

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

Arg Met Phe Leu Lys Val Arg Glu Ser Asn Thr Thr Glu Cys Asp Ser
                965                 970                 975

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

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

Arg Ala  Val Leu Gly Glu Val  Lys Ser Cys Thr Trp  Pro Glu Thr
    1010                1015                1020

His Thr  Leu Trp Gly Asp Gly  Ile Leu Glu Ser Asp  Leu Ile Ile
    1025                1030                1035
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Pro Val  Thr Leu Ala Gly Pro  Arg Ser Asn His Asn  Arg Arg Pro
    1040                 1045                 1050

Gly Tyr  Lys Thr Gln Asn Gln  Gly Pro Trp Asp Glu  Gly Arg Val
    1055                 1060                 1065

Glu Ile  Asp Phe Asp Tyr Cys  Pro Gly Thr Thr Val  Thr Leu Ser
    1070                 1075                 1080

Glu Ser  Cys Gly His Arg Gly  Pro Ala Thr Arg Thr  Thr Thr Glu
    1085                 1090                 1095

Ser Gly  Lys Leu Ile Thr Asp  Trp Cys Cys Arg Ser  Cys Thr Leu
    1100                 1105                 1110

Pro Pro  Leu Arg Tyr Gln Thr  Asp Ser Gly Cys Trp  Tyr Gly Met
    1115                 1120                 1125

Glu Ile  Arg Pro Gln Arg His  Asp Glu Lys Thr Leu  Val Gln Ser
    1130                 1135                 1140

Gln Val  Asn Ala Tyr Asn Ala  Asp Met Ile Asp Pro  Phe Gln Leu
    1145                 1150                 1155

Gly Leu  Leu Val Val Phe Leu  Ala Thr Gln Glu Val  Leu Arg Lys
    1160                 1165                 1170

Arg Trp  Thr Ala Lys Ile Ser  Met Pro Ala Ile Leu  Ile Ala Leu
    1175                 1180                 1185

Leu Val  Leu Val Phe Gly Gly  Ile Thr Tyr Thr Asp  Val Leu Arg
    1190                 1195                 1200

Tyr Val  Ile Leu Val Gly Ala  Ala Phe Ala Glu Ser  Asn Ser Gly
    1205                 1210                 1215

Gly Asp  Val Val His Leu Ala  Leu Met Ala Thr Phe  Lys Ile Gln
    1220                 1225                 1230

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

Gln Glu  Asn Ile Leu Leu Met  Leu Ala Ala Val Phe  Phe Gln Met
    1250                 1255                 1260

Ala Tyr  Tyr Asp Ala Arg Gln  Ile Leu Leu Trp Glu  Ile Pro Asp
    1265                 1270                 1275

Val Leu  Asn Ser Leu Ala Val  Ala Trp Met Ile Leu  Arg Ala Ile
    1280                 1285                 1290

Thr Phe  Thr Thr Thr Ser Asn  Val Val Val Pro Leu  Leu Ala Leu
    1295                 1300                 1305

Leu Thr  Pro Gly Leu Arg Cys  Leu Asn Leu Asp Val  Tyr Arg Ile
    1310                 1315                 1320

Leu Leu  Leu Met Val Gly Ile  Gly Ser Leu Ile Arg  Glu Lys Arg
    1325                 1330                 1335

Ser Ala  Ala Ala Lys Lys Lys  Gly Ala Ser Leu Leu  Cys Leu Ala
    1340                 1345                 1350

Leu Ala  Ser Thr Gly Leu Phe  Asn Pro Met Ile Leu  Ala Ala Gly
    1355                 1360                 1365

Leu Ile  Ala Cys Asp Pro Asn  Arg Lys Arg Gly Trp  Pro Ala Thr
    1370                 1375                 1380

Glu Val  Met Thr Ala Val Gly  Leu Met Phe Ala Ile  Val Gly Gly
    1385                 1390                 1395

Leu Ala  Glu Leu Asp Ile Asp  Ser Met Ala Ile Pro  Met Thr Ile
    1400                 1405                 1410

Ala Gly  Leu Met Phe Ala Ala  Phe Val Ile Ser Gly  Lys Ser Thr
    1415                 1420                 1425
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Asp Met  Trp Ile Glu Arg Thr  Ala Asp Ile Ser Trp  Glu Ser Asp
    1430                 1435                 1440

Ala Glu  Ile Thr Gly Ser Ser  Glu Arg Val Asp Val  Arg Leu Asp
    1445                 1450                 1455

Asp Asp  Gly Asn Phe Gln Leu  Met Asn Asp Pro Gly  Ala Pro Trp
    1460                 1465                 1470

Lys Ile  Trp Met Leu Arg Met  Val Cys Leu Ala Ile  Ser Ala Tyr
    1475                 1480                 1485

Thr Pro  Trp Ala Ile Leu Pro  Ser Val Val Gly Phe  Trp Ile Thr
    1490                 1495                 1500

Leu Gln  Tyr Thr Lys Arg Gly  Gly Val Leu Trp Asp  Thr Pro Ser
    1505                 1510                 1515

Pro Lys  Glu Tyr Lys Lys Gly  Asp Thr Thr Thr Gly  Val Tyr Arg
    1520                 1525                 1530

Ile Met  Thr Arg Gly Leu Leu  Gly Ser Tyr Gln Ala  Gly Ala Gly
    1535                 1540                 1545

Val Met  Val Glu Gly Val Phe  His Thr Leu Trp His  Thr Thr Lys
    1550                 1555                 1560

Gly Ala  Ala Leu Met Ser Gly  Glu Gly Arg Leu Asp  Pro Tyr Trp
    1565                 1570                 1575

Gly Ser  Val Lys Glu Asp Arg  Leu Cys Tyr Gly Gly  Pro Trp Lys
    1580                 1585                 1590

Leu Gln  His Lys Trp Asn Gly  Gln Asp Glu Val Gln  Met Ile Val
    1595                 1600                 1605

Val Glu  Pro Gly Arg Asn Val  Lys Asn Val Gln Thr  Lys Pro Gly
    1610                 1615                 1620

Val Phe  Lys Thr Pro Glu Gly  Glu Ile Gly Ala Val  Thr Leu Asp
    1625                 1630                 1635

Phe Pro  Thr Gly Thr Ser Gly  Ser Pro Ile Val Asp  Lys Asn Gly
    1640                 1645                 1650

Asp Val  Ile Gly Leu Tyr Gly  Asn Gly Val Ile Met  Pro Asn Gly
    1655                 1660                 1665

Ser Tyr  Ile Ser Ala Ile Val  Gln Gly Glu Arg Met  Asp Glu Pro
    1670                 1675                 1680

Ile Pro  Ala Gly Phe Glu Pro  Glu Met Leu Arg Lys  Lys Gln Ile
    1685                 1690                 1695

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

Leu Pro  Gln Ile Ile Lys Glu  Ala Ile Asn Arg Arg  Leu Arg Thr
    1715                 1720                 1725

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

Ala Leu  Arg Gly Leu Pro Ile  Arg Tyr Gln Thr Ser  Ala Val Pro
    1745                 1750                 1755

Arg Glu  His Asn Gly Asn Glu  Ile Val Asp Val Met  Cys His Ala
    1760                 1765                 1770

Thr Leu  Thr His Arg Leu Met  Ser Pro His Arg Val  Pro Asn Tyr
    1775                 1780                 1785

Asn Leu  Phe Val Met Asp Glu  Ala His Phe Thr Asp  Pro Ala Ser
    1790                 1795                 1800

Ile Ala  Ala Arg Gly Tyr Ile  Ser Thr Lys Val Glu  Leu Gly Glu
    1805                 1810                 1815

Ala Ala  Ala Ile Phe Met Thr  Ala Thr Pro Pro Gly  Thr Ser Asp
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    1820                1825                1830

Pro Phe  Pro Glu Ser Asn Ser  Pro Ile Ser Asp Leu  Gln Thr Glu
    1835                1840                1845

Ile Pro  Asp Arg Ala Trp Asn  Ser Gly Tyr Glu Trp  Ile Thr Glu
    1850                1855                1860

Tyr Thr  Gly Lys Thr Val Trp  Phe Val Pro Ser Val  Lys Met Gly
    1865                1870                1875

Asn Glu  Ile Ala Leu Cys Leu  Gln Arg Ala Gly Lys  Lys Val Val
    1880                1885                1890

Gln Leu  Asn Arg Lys Ser Tyr  Glu Thr Glu Tyr Pro  Lys Cys Lys
    1895                1900                1905

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

Gly Ala  Asn Phe Lys Ala Ser  Arg Val Ile Asp Ser  Arg Lys Ser
    1925                1930                1935

Val Lys  Pro Thr Ile Ile Thr  Glu Gly Glu Gly Arg  Val Ile Leu
    1940                1945                1950

Gly Glu  Pro Ser Ala Val Thr  Ala Ala Ser Ala Ala  Gln Arg Arg
    1955                1960                1965

Gly Arg  Ile Gly Arg Asn Pro  Ser Gln Val Gly Asp  Glu Tyr Cys
    1970                1975                1980

Tyr Gly  Gly His Thr Asn Glu  Asp Asp Ser Asn Phe  Ala His Trp
    1985                1990                1995

Thr Glu  Ala Arg Ile Met Leu  Asp Asn Ile Asn Met  Pro Asn Gly
    2000                2005                2010

Leu Ile  Ala Gln Phe Tyr Gln  Pro Glu Arg Glu Lys  Val Tyr Thr
    2015                2020                2025

Met Asp  Gly Glu Tyr Arg Leu  Arg Gly Glu Glu Arg  Lys Asn Phe
    2030                2035                2040

Leu Glu  Leu Leu Arg Thr Ala  Asp Leu Pro Val Trp  Leu Ala Tyr
    2045                2050                2055

Lys Val  Ala Ala Ala Gly Val  Ser Tyr His Asp Arg  Arg Trp Cys
    2060                2065                2070

Phe Asp  Gly Pro Arg Thr Asn  Thr Ile Leu Glu Asp  Asn Asn Glu
    2075                2080                2085

Val Glu  Val Ile Thr Lys Leu  Gly Glu Arg Lys Ile  Leu Arg Pro
    2090                2095                2100

Arg Trp  Ile Asp Ala Arg Val  Tyr Ser Asp His Gln  Ala Leu Lys
    2105                2110                2115

Ala Phe  Lys Asp Phe Ala Ser  Gly Lys Arg Ser Gln  Ile Gly Leu
    2120                2125                2130

Ile Glu  Val Leu Gly Lys Met  Pro Glu His Phe Met  Gly Lys Thr
    2135                2140                2145

Trp Glu  Ala Leu Asp Thr Met  Tyr Val Val Ala Thr  Ala Glu Lys
    2150                2155                2160

Gly Gly  Arg Ala His Arg Met  Ala Leu Glu Glu Leu  Pro Asp Ala
    2165                2170                2175

Leu Gln  Thr Ile Ala Leu Ile  Ala Leu Leu Ser Val  Met Thr Met
    2180                2185                2190

Gly Val  Phe Phe Leu Leu Met  Gln Arg Lys Gly Ile  Gly Lys Ile
    2195                2200                2205

Gly Leu  Gly Gly Ala Val Leu  Gly Val Ala Thr Phe  Phe Cys Trp
    2210                2215                2220
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Met Ala  Glu Val Pro Gly Thr  Lys Ile Ala Gly Met  Leu Leu Leu
    2225                 2230                 2235

Ser Leu  Leu Leu Met Ile Val  Leu Ile Pro Glu Pro  Glu Lys Gln
    2240                 2245                 2250

Arg Ser  Gln Thr Asp Asn Gln  Leu Ala Val Phe Leu  Ile Cys Val
    2255                 2260                 2265

Met Thr  Leu Val Ser Ala Val  Ala Ala Asn Glu Met  Gly Trp Leu
    2270                 2275                 2280

Asp Lys  Thr Lys Ser Asp Ile  Ser Ser Leu Phe Gly  Gln Arg Ile
    2285                 2290                 2295

Glu Val  Lys Glu Asn Phe Ser  Met Gly Glu Phe Leu  Leu Asp Leu
    2300                 2305                 2310

Arg Pro  Ala Thr Ala Trp Ser  Leu Tyr Ala Val Thr  Thr Ala Val
    2315                 2320                 2325

Leu Thr  Pro Leu Leu Lys His  Leu Ile Thr Ser Asp  Tyr Ile Asn
    2330                 2335                 2340

Thr Ser  Leu Thr Ser Ile Asn  Val Gln Ala Ser Ala  Leu Phe Thr
    2345                 2350                 2355

Leu Ala  Arg Gly Phe Pro Phe  Val Asp Val Gly Val  Ser Ala Leu
    2360                 2365                 2370

Leu Leu  Ala Ala Gly Cys Trp  Gly Gln Val Thr Leu  Thr Val Thr
    2375                 2380                 2385

Val Thr  Ala Ala Thr Leu Leu  Phe Cys His Tyr Ala  Tyr Met Val
    2390                 2395                 2400

Pro Gly  Trp Gln Ala Glu Ala  Met Arg Ser Ala Gln  Arg Arg Thr
    2405                 2410                 2415

Ala Ala  Gly Ile Met Lys Asn  Ala Val Val Asp Gly  Ile Val Ala
    2420                 2425                 2430

Thr Asp  Val Pro Glu Leu Glu  Arg Thr Thr Pro Ile  Met Gln Lys
    2435                 2440                 2445

Lys Val  Gly Gln Ile Met Leu  Ile Leu Val Ser Leu  Ala Ala Val
    2450                 2455                 2460

Val Val  Asn Pro Ser Val Lys  Thr Val Arg Glu Ala  Gly Ile Leu
    2465                 2470                 2475

Ile Thr  Ala Ala Ala Val Thr  Leu Trp Glu Asn Gly  Ala Ser Ser
    2480                 2485                 2490

Val Trp  Asn Ala Thr Thr Ala  Ile Gly Leu Cys His  Ile Met Arg
    2495                 2500                 2505

Gly Gly  Trp Leu Ser Cys Leu  Ser Ile Thr Trp Thr  Leu Ile Lys
    2510                 2515                 2520

Asn Met  Glu Lys Pro Gly Leu  Lys Arg Gly Gly Ala  Lys Gly Arg
    2525                 2530                 2535

Thr Leu  Gly Glu Val Trp Lys  Glu Arg Leu Asn Gln  Met Thr Lys
    2540                 2545                 2550

Glu Glu  Phe Thr Arg Tyr Arg  Lys Glu Ala Ile Ile  Glu Val Asp
    2555                 2560                 2565

Arg Ser  Ala Ala Lys His Ala  Arg Lys Glu Gly Asn  Val Thr Gly
    2570                 2575                 2580

Gly His  Pro Val Ser Arg Gly  Thr Ala Lys Leu Arg  Trp Leu Val
    2585                 2590                 2595

Glu Arg  Arg Phe Leu Glu Pro  Val Gly Lys Val Ile  Asp Leu Gly
    2600                 2605                 2610
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Cys Gly  Arg Gly Gly Trp Cys  Tyr Tyr Met Ala Thr  Gln Lys Arg
    2615                 2620                 2625

Val Gln  Glu Val Arg Gly Tyr  Thr Lys Gly Gly Pro  Gly His Glu
    2630                 2635                 2640

Glu Pro  Gln Leu Val Gln Ser  Tyr Gly Trp Asn Ile  Val Thr Met
    2645                 2650                 2655

Lys Ser  Gly Val Asp Val Phe  Tyr Arg Pro Ser Glu  Cys Cys Asp
    2660                 2665                 2670

Thr Leu  Leu Cys Asp Ile Gly  Glu Ser Ser Ser Ser  Ala Glu Val
    2675                 2680                 2685

Glu Glu  His Arg Thr Ile Arg  Val Leu Glu Met Val  Glu Asp Trp
    2690                 2695                 2700

Leu His  Arg Gly Pro Arg Glu  Phe Cys Val Lys Val  Leu Cys Pro
    2705                 2710                 2715

Tyr Met  Pro Lys Val Ile Glu  Lys Met Glu Leu Leu  Gln Arg Arg
    2720                 2725                 2730

Tyr Gly  Gly Gly Leu Val Arg  Asn Pro Leu Ser Arg  Asn Ser Thr
    2735                 2740                 2745

His Glu  Met Tyr Trp Val Ser  Arg Ala Ser Gly Asn  Val Val His
    2750                 2755                 2760

Ser Val  Asn Met Thr Ser Gln  Val Leu Leu Gly Arg  Met Glu Lys
    2765                 2770                 2775

Arg Thr  Trp Lys Gly Pro Gln  Tyr Glu Glu Asp Val  Asn Leu Gly
    2780                 2785                 2790

Ser Gly  Thr Arg Ala Val Gly  Lys Pro Leu Leu Asn  Ser Asp Thr
    2795                 2800                 2805

Ser Lys  Ile Lys Asn Arg Ile  Glu Arg Leu Arg Arg  Glu Tyr Ser
    2810                 2815                 2820

Ser Thr  Trp His His Asp Glu  Asn His Pro Tyr Arg  Thr Trp Asn
    2825                 2830                 2835

Tyr His  Gly Ser Tyr Asp Val  Lys Pro Thr Gly Ser  Ala Ser Ser
    2840                 2845                 2850

Leu Val  Asn Gly Val Val Arg  Leu Leu Ser Lys Pro  Trp Asp Thr
    2855                 2860                 2865

Ile Thr  Asn Val Thr Thr Met  Ala Met Thr Asp Thr  Thr Pro Phe
    2870                 2875                 2880

Gly Gln  Gln Arg Val Phe Lys  Glu Lys Val Asp Thr  Lys Ala Pro
    2885                 2890                 2895

Glu Pro  Pro Glu Gly Val Lys  Tyr Val Leu Asn Glu  Thr Thr Asn
    2900                 2905                 2910

Trp Leu  Trp Ala Phe Leu Ala  Arg Glu Lys Arg Pro  Arg Met Cys
    2915                 2920                 2925

Ser Arg  Glu Glu Phe Ile Arg  Lys Val Asn Ser Asn  Ala Ala Leu
    2930                 2935                 2940

Gly Ala  Met Phe Glu Glu Gln  Asn Gln Trp Arg Ser  Ala Arg Glu
    2945                 2950                 2955

Ala Val  Glu Asp Pro Lys Phe  Trp Glu Met Val Asp  Glu Glu Arg
    2960                 2965                 2970

Glu Ala  His Leu Arg Gly Glu  Cys His Thr Cys Ile  Tyr Asn Met
    2975                 2980                 2985

Met Gly  Lys Arg Glu Lys Lys  Pro Gly Glu Phe Gly  Lys Ala Lys
    2990                 2995                 3000

Gly Ser  Arg Ala Ile Trp Phe  Met Trp Leu Gly Ala  Arg Phe Leu
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    3005                3010                3015

Glu Phe  Glu Ala Leu Gly Phe  Leu Asn Glu Asp His  Trp Leu Gly
    3020                3025                3030

Arg Lys  Asn Ser Gly Gly Gly  Val Glu Gly Leu Gly  Leu Gln Lys
    3035                3040                3045

Leu Gly  Tyr Ile Leu Arg Glu  Val Gly Thr Arg Pro  Gly Gly Lys
    3050                3055                3060

Ile Tyr  Ala Asp Asp Thr Ala  Gly Trp Asp Thr Arg  Ile Thr Arg
    3065                3070                3075

Ala Asp  Leu Glu Asn Glu Ala  Lys Val Leu Glu Leu  Leu Asp Gly
    3080                3085                3090

Glu His  Arg Arg Leu Ala Arg  Ala Ile Ile Glu Leu  Thr Tyr Arg
    3095                3100                3105

His Lys  Val Val Lys Val Met  Arg Pro Ala Ala Asp  Gly Arg Thr
    3110                3115                3120

Val Met  Asp Val Ile Ser Arg  Glu Asp Gln Arg Gly  Ser Gly Gln
    3125                3130                3135

Val Val  Thr Tyr Ala Leu Asn  Thr Phe Thr Asn Leu  Ala Val Gln
    3140                3145                3150

Leu Val  Arg Met Met Glu Gly  Glu Gly Val Ile Gly  Pro Asp Asp
    3155                3160                3165

Val Glu  Lys Leu Thr Lys Gly  Lys Gly Pro Lys Val  Arg Thr Trp
    3170                3175                3180

Leu Phe  Glu Asn Gly Glu Glu  Arg Leu Ser Arg Met  Ala Val Ser
    3185                3190                3195

Gly Asp  Asp Cys Val Val Lys  Pro Leu Asp Asp Arg  Phe Ala Thr
    3200                3205                3210

Ser Leu  His Phe Leu Asn Ala  Met Ser Lys Val Arg  Lys Asp Ile
    3215                3220                3225

Gln Glu  Trp Lys Pro Ser Thr  Gly Trp Tyr Asp Trp  Gln Gln Val
    3230                3235                3240

Pro Phe  Cys Ser Asn His Phe  Thr Glu Leu Ile Met  Lys Asp Gly
    3245                3250                3255

Arg Thr  Leu Val Val Pro Cys  Arg Gly Gln Asp Glu  Leu Val Gly
    3260                3265                3270

Arg Ala  Arg Ile Ser Pro Gly  Ala Gly Trp Asn Val  Arg Asp Thr
    3275                3280                3285

Ala Cys  Leu Ala Lys Ser Tyr  Ala Gln Met Trp Leu  Leu Leu Tyr
    3290                3295                3300

Phe His  Arg Arg Asp Leu Arg  Leu Met Ala Asn Ala  Ile Cys Ser
    3305                3310                3315

Ala Val  Pro Val Asn Trp Val  Pro Thr Gly Arg Thr  Thr Trp Ser
    3320                3325                3330

Ile His  Ala Gly Gly Glu Trp  Met Thr Thr Glu Asp  Met Leu Glu
    3335                3340                3345

Val Trp  Asn Arg Val Trp Ile  Glu Glu Asn Glu Trp  Met Glu Asp
    3350                3355                3360

Lys Thr  Pro Val Glu Lys Trp  Ser Asp Val Pro Tyr  Ser Gly Lys
    3365                3370                3375

Arg Glu  Asp Ile Trp Cys Gly  Ser Leu Ile Gly Thr  Arg Ala Arg
    3380                3385                3390

Ala Thr  Trp Ala Glu Asn Ile  Gln Val Ala Ile Asn  Gln Val Arg
    3395                3400                3405
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Ala Ile  Ile Gly Asp Glu Lys  Tyr Val Asp Tyr Met  Ser Ser Leu
    3410                 3415                 3420

Lys Arg  Tyr Glu Asp Thr Thr  Leu Val Glu Asp Thr  Val Leu
    3425                 3430                 3435


<210> SEQ ID NO 5
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705                 710                 715                 720

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

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

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

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

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

Ile Asp Ile Ser Arg Gln Glu Leu Arg Cys Gly Ser Gly Val Phe Ile
                805                 810                 815

His Asn Asp Val Glu Ala Trp Met Asp Arg Tyr Lys Tyr Tyr Pro Glu
            820                 825                 830
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Thr Pro Gln Gly Leu Ala Lys Ile Ile Gln Lys Ala His Lys Glu Gly
        835                 840                 845

Val Cys Gly Leu Arg Ser Val Ser Arg Leu Glu His Gln Met Trp Glu
    850                 855                 860

Ala Val Lys Asp Glu Leu Asn Thr Leu Leu Lys Glu Asn Gly Val Asp
865                 870                 875                 880

Leu Ser Val Val Val Glu Lys Gln Glu Gly Met Tyr Lys Ser Ala Pro
                885                 890                 895

Lys Arg Leu Thr Ala Thr Thr Glu Lys Leu Glu Ile Gly Trp Lys Ala
            900                 905                 910

Trp Gly Lys Ser Ile Leu Phe Ala Pro Glu Leu Ala Asn Asn Thr Phe
        915                 920                 925

Val Val Asp Gly Pro Glu Thr Lys Glu Cys Pro Thr Gln Asn Arg Ala
    930                 935                 940

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

Arg Met Phe Leu Lys Val Arg Glu Ser Asn Thr Thr Glu Cys Asp Ser
                965                 970                 975

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

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

Arg Ala  Val Leu Gly Glu Val  Lys Ser Cys Thr Trp  Pro Glu Thr
    1010                 1015                 1020

His Thr  Leu Trp Gly Asp Gly  Ile Leu Glu Ser Asp  Leu Ile Ile
    1025                 1030                 1035

Pro Val  Thr Leu Ala Gly Pro  Arg Ser Asn His Asn  Arg Arg Pro
    1040                 1045                 1050

Gly Tyr  Lys Thr Gln Asn Gln  Gly Pro Trp Asp Glu  Gly Arg Val
    1055                 1060                 1065

Glu Ile  Asp Phe Asp Tyr Cys  Pro Gly Thr Thr Val  Thr Leu Ser
    1070                 1075                 1080

Glu Ser  Cys Gly His Arg Gly  Pro Ala Thr Arg Thr  Thr Thr Glu
    1085                 1090                 1095

Ser Gly  Lys Leu Ile Thr Asp  Trp Cys Cys Arg Ser  Cys Thr Leu
    1100                 1105                 1110

Pro Pro  Leu Arg Tyr Gln Thr  Asp Ser Gly Cys Trp  Tyr Gly Met
    1115                 1120                 1125

Glu Ile  Arg Pro Gln Arg His  Asp Glu Lys Thr Leu  Val Gln Ser
    1130                 1135                 1140

Gln Val  Asn Ala Tyr Asn Ala  Asp Met Ile Asp Pro  Phe Gln Leu
    1145                 1150                 1155

Gly Leu  Leu Val Val Phe Leu  Ala Thr Gln Glu Val  Leu Arg Lys
    1160                 1165                 1170

Arg Trp  Thr Ala Lys Ile Ser  Met Pro Ala Ile Leu  Ile Ala Leu
    1175                 1180                 1185

Leu Val  Leu Val Phe Gly Gly  Ile Thr Tyr Thr Asp  Val Leu Arg
    1190                 1195                 1200

Tyr Val  Ile Leu Val Gly Ala  Ala Phe Ala Glu Ser  Asn Ser Gly
    1205                 1210                 1215

Gly Asp  Val Val His Leu Ala  Leu Met Ala Thr Phe  Lys Ile Gln
    1220                 1225                 1230

Pro Val  Phe Met Val Ala Ser  Phe Leu Lys Ala Arg  Trp Thr Asn
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Gln Glu Asn Ile Leu Leu Met Leu Ala Ala Val Phe Phe Gln Met
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Ala Tyr Tyr Asp Ala Arg Gln Ile Leu Leu Trp Glu Ile Pro Asp
1265 1270 1275

Val Leu Asn Ser Leu Ala Val Ala Trp Met Ile Leu Arg Ala Ile
1280 1285 1290

Thr Phe Thr Thr Thr Ser Asn Val Val Val Pro Leu Leu Ala Leu
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Leu Thr Pro Gly Leu Arg Cys Leu Asn Leu Asp Val Tyr Arg Ile
1310 1315 1320

Leu Leu Leu Met Val Gly Ile Gly Ser Leu Ile Arg Glu Lys Arg
1325 1330 1335

Ser Ala Ala Ala Lys Lys Lys Gly Ala Ser Leu Leu Cys Leu Ala
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Leu Ala Ser Thr Gly Leu Phe Asn Pro Met Ile Leu Ala Ala Gly
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Leu Ile Ala Cys Asp Pro Asn Arg Lys Arg Gly Trp Pro Ala Thr
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Glu Val Met Thr Ala Val Gly Leu Met Phe Ala Ile Val Gly Gly
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Leu Ala Glu Leu Asp Ile Asp Ser Met Ala Ile Pro Met Thr Ile
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Ala Gly Leu Met Phe Ala Ala Phe Val Ile Ser Gly Lys Ser Thr
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Asp Met Trp Ile Glu Arg Thr Ala Asp Ile Ser Trp Glu Ser Asp
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Ala Glu Ile Thr Gly Ser Ser Glu Arg Val Asp Val Arg Leu Asp
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Asp Asp Gly Asn Phe Gln Leu Met Asn Asp Pro Gly Ala Pro Trp
1460 1465 1470

Lys Ile Trp Met Leu Arg Met Val Cys Leu Ala Ile Ser Ala Tyr
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Thr Pro Trp Ala Ile Leu Pro Ser Val Val Gly Phe Trp Ile Thr
1490 1495 1500

Leu Gln Tyr Thr Lys Arg Gly Gly Val Leu Trp Asp Thr Pro Ser
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Pro Lys Glu Tyr Lys Lys Gly Asp Thr Thr Thr Gly Val Tyr Arg
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Ile Met Thr Arg Gly Leu Leu Gly Ser Tyr Gln Ala Gly Ala Gly
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Val Met Val Glu Gly Val Phe His Thr Leu Trp His Thr Thr Lys
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Gly Ala Ala Leu Met Ser Gly Glu Gly Arg Leu Asp Pro Tyr Trp
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Gly Ser Val Lys Glu Asp Arg Leu Cys Tyr Gly Gly Pro Trp Lys
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Leu Gln His Lys Trp Asn Gly Gln Asp Glu Val Gln Met Ile Val
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Val Glu Pro Gly Arg Asn Val Lys Asn Val Gln Thr Lys Pro Gly
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Val Phe Lys Thr Pro Glu Gly Glu Ile Gly Ala Val Thr Leu Asp
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Phe Pro Thr Gly Thr Ser Gly Ser Pro Ile Val Asp Lys Asn Gly
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Asp Val Ile Gly Leu Tyr Gly Asn Gly Val Ile Met Pro Asn Gly
1655 1660 1665

Ser Tyr Ile Ser Ala Ile Val Gln Gly Glu Arg Met Asp Glu Pro
1670 1675 1680

Ile Pro Ala Gly Phe Glu Pro Glu Met Leu Arg Lys Lys Gln Ile
1685 1690 1695

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

Leu Pro Gln Ile Ile Lys Glu Ala Ile Asn Arg Arg Leu Arg Thr
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Ala Val Leu Ala Pro Thr Arg Val Val Ala Ala Glu Met Ala Glu
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Ala Leu Arg Gly Leu Pro Ile Arg Tyr Gln Thr Ser Ala Val Pro
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Arg Glu His Asn Gly Asn Glu Ile Val Asp Val Met Cys His Ala
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Thr Leu Thr His Arg Leu Met Ser Pro His Arg Val Pro Asn Tyr
1775 1780 1785

Asn Leu Phe Val Met Asp Glu Ala His Phe Thr Asp Pro Ala Ser
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Ile Ala Ala Arg Gly Tyr Ile Ser Thr Lys Val Glu Leu Gly Glu
1805 1810 1815

Ala Ala Ala Ile Phe Met Thr Ala Thr Pro Pro Gly Thr Ser Asp
1820 1825 1830

Pro Phe Pro Glu Ser Asn Ser Pro Ile Ser Asp Leu Gln Thr Glu
1835 1840 1845

Ile Pro Asp Arg Ala Trp Asn Ser Gly Tyr Glu Trp Ile Thr Glu
1850 1855 1860

Tyr Thr Gly Lys Thr Val Trp Phe Val Pro Ser Val Lys Met Gly
1865 1870 1875

Asn Glu Ile Ala Leu Cys Leu Gln Arg Ala Gly Lys Lys Val Val
1880 1885 1890

Gln Leu Asn Arg Lys Ser Tyr Glu Thr Glu Tyr Pro Lys Cys Lys
1895 1900 1905

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

Gly Ala Asn Phe Lys Ala Ser Arg Val Ile Asp Ser Arg Lys Ser
1925 1930 1935

Val Lys Pro Thr Ile Ile Thr Glu Gly Glu Gly Arg Val Ile Leu
1940 1945 1950

Gly Glu Pro Ser Ala Val Thr Ala Ala Ser Ala Ala Gln Arg Arg
1955 1960 1965

Gly Arg Ile Gly Arg Asn Pro Ser Gln Val Gly Asp Glu Tyr Cys
1970 1975 1980

Tyr Gly Gly His Thr Asn Glu Asp Asp Ser Asn Phe Ala His Trp
1985 1990 1995

Thr Glu Ala Arg Ile Met Leu Asp Asn Ile Asn Met Pro Asn Gly
2000 2005 2010

Leu Ile Ala Gln Phe Tyr Gln Pro Glu Arg Glu Lys Val Tyr Thr
2015 2020 2025

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Met Asp  Gly Glu Tyr Arg Leu  Arg Gly Glu Glu Arg  Lys Asn Phe
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Leu Glu  Leu Leu Arg Thr Ala  Asp Leu Pro Val Trp  Leu Ala Tyr
    2045                 2050                 2055

Lys Val  Ala Ala Ala Gly Val  Ser Tyr His Asp Arg  Arg Trp Cys
    2060                 2065                 2070

Phe Asp  Gly Pro Arg Thr Asn  Thr Ile Leu Glu Asp  Asn Asn Glu
    2075                 2080                 2085

Val Glu  Val Ile Thr Lys Leu  Gly Glu Arg Lys Ile  Leu Arg Pro
    2090                 2095                 2100

Arg Trp  Ile Asp Ala Arg Val  Tyr Ser Asp His Gln  Ala Leu Lys
    2105                 2110                 2115

Ala Phe  Lys Asp Phe Ala Ser  Gly Lys Arg Ser Gln  Ile Gly Leu
    2120                 2125                 2130

Ile Glu  Val Leu Gly Lys Met  Pro Glu His Phe Met  Gly Lys Thr
    2135                 2140                 2145

Trp Glu  Ala Leu Asp Thr Met  Tyr Val Val Ala Thr  Ala Glu Lys
    2150                 2155                 2160

Gly Gly  Arg Ala His Arg Met  Ala Leu Glu Glu Leu  Pro Asp Ala
    2165                 2170                 2175

Leu Gln  Thr Ile Ala Leu Ile  Ala Leu Leu Ser Val  Met Thr Met
    2180                 2185                 2190

Gly Val  Phe Phe Leu Leu Met  Gln Arg Lys Gly Ile  Gly Lys Ile
    2195                 2200                 2205

Gly Leu  Gly Gly Ala Val Leu  Gly Val Ala Thr Phe  Phe Cys Trp
    2210                 2215                 2220

Met Ala  Glu Val Pro Gly Thr  Lys Ile Ala Gly Met  Leu Leu Leu
    2225                 2230                 2235

Ser Leu  Leu Leu Met Ile Val  Leu Ile Pro Glu Pro  Glu Lys Gln
    2240                 2245                 2250

Arg Ser  Gln Thr Asp Asn Gln  Leu Ala Val Phe Leu  Ile Cys Val
    2255                 2260                 2265

Met Thr  Leu Val Ser Ala Val  Ala Ala Asn Glu Met  Gly Trp Leu
    2270                 2275                 2280

Asp Lys  Thr Lys Ser Asp Ile  Ser Ser Leu Phe Gly  Gln Arg Ile
    2285                 2290                 2295

Glu Val  Lys Glu Asn Phe Ser  Met Gly Glu Phe Leu  Leu Asp Leu
    2300                 2305                 2310

Arg Pro  Ala Thr Ala Trp Ser  Leu Tyr Ala Val Thr  Thr Ala Val
    2315                 2320                 2325

Leu Thr  Pro Leu Leu Lys His  Leu Ile Thr Ser Asp  Tyr Ile Asn
    2330                 2335                 2340

Thr Ser  Leu Thr Ser Ile Asn  Val Gln Ala Ser Ala  Leu Phe Thr
    2345                 2350                 2355

Leu Ala  Arg Gly Phe Pro Phe  Val Asp Val Gly Val  Ser Ala Leu
    2360                 2365                 2370

Leu Leu  Ala Ala Gly Cys Trp  Gly Gln Val Thr Leu  Thr Val Thr
    2375                 2380                 2385

Val Thr  Ala Ala Thr Leu Leu  Phe Cys His Tyr Ala  Tyr Met Val
    2390                 2395                 2400

Pro Gly  Trp Gln Ala Glu Ala  Met Arg Ser Ala Gln  Arg Arg Thr
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Ala Ala  Gly Ile Met Lys Asn  Ala Val Val Asp Gly  Ile Val Ala
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    2420                2425                2430

Thr Asp  Val Pro Glu Leu Glu  Arg Thr Thr Pro Ile  Met Gln Lys
    2435                2440                2445

Lys Val  Gly Gln Ile Met Leu  Ile Leu Val Ser Leu  Ala Ala Val
    2450                2455                2460

Val Val  Asn Pro Ser Val Lys  Thr Val Arg Glu Ala  Gly Ile Leu
    2465                2470                2475

Ile Thr  Ala Ala Ala Val Thr  Leu Trp Glu Asn Gly  Ala Ser Ser
    2480                2485                2490

Val Trp  Asn Ala Thr Thr Ala  Ile Gly Leu Cys His  Ile Met Arg
    2495                2500                2505

Gly Gly  Trp Leu Ser Cys Leu  Ser Ile Thr Trp Thr  Leu Ile Lys
    2510                2515                2520

Asn Met  Glu Lys Pro Gly Leu  Lys Arg Gly Gly Ala  Lys Gly Arg
    2525                2530                2535

Thr Leu  Gly Glu Val Trp Lys  Glu Arg Leu Asn Gln  Met Thr Lys
    2540                2545                2550

Glu Glu  Phe Thr Arg Tyr Arg  Lys Glu Ala Ile Ile  Glu Val Asp
    2555                2560                2565

Arg Ser  Ala Ala Lys His Ala  Arg Lys Glu Gly Asn  Val Thr Gly
    2570                2575                2580

Gly His  Pro Val Ser Arg Gly  Thr Ala Lys Leu Arg  Trp Leu Val
    2585                2590                2595

Glu Arg  Arg Phe Leu Glu Pro  Val Gly Lys Val Ile  Asp Leu Gly
    2600                2605                2610

Cys Gly  Arg Gly Gly Trp Cys  Tyr Tyr Met Ala Thr  Gln Lys Arg
    2615                2620                2625

Val Gln  Glu Val Arg Gly Tyr  Thr Lys Gly Gly Pro  Gly His Glu
    2630                2635                2640

Glu Pro  Gln Leu Val Gln Ser  Tyr Gly Trp Asn Ile  Val Thr Met
    2645                2650                2655

Lys Ser  Gly Val Asp Val Phe  Tyr Arg Pro Ser Glu  Cys Cys Asp
    2660                2665                2670

Thr Leu  Leu Cys Asp Ile Gly  Glu Ser Ser Ser Ser  Ala Glu Val
    2675                2680                2685

Glu Glu  His Arg Thr Ile Arg  Val Leu Glu Met Val  Glu Asp Trp
    2690                2695                2700

Leu His  Arg Gly Pro Arg Glu  Phe Cys Val Lys Val  Leu Cys Pro
    2705                2710                2715

Tyr Met  Pro Lys Val Ile Glu  Lys Met Glu Leu Leu  Gln Arg Arg
    2720                2725                2730

Tyr Gly  Gly Gly Leu Val Arg  Asn Pro Leu Ser Arg  Asn Ser Thr
    2735                2740                2745

His Glu  Met Tyr Trp Val Ser  Arg Ala Ser Gly Asn  Val Val His
    2750                2755                2760

Ser Val  Asn Met Thr Ser Gln  Val Leu Leu Gly Arg  Met Glu Lys
    2765                2770                2775

Arg Thr  Trp Lys Gly Pro Gln  Tyr Glu Glu Asp Val  Asn Leu Gly
    2780                2785                2790

Ser Gly  Thr Arg Ala Val Gly  Lys Pro Leu Leu Asn  Ser Asp Thr
    2795                2800                2805

Ser Lys  Ile Lys Asn Arg Ile  Glu Arg Leu Arg Arg  Glu Tyr Ser
    2810                2815                2820
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Ser Thr Trp His His Asp Glu Asn His Pro Tyr Arg Thr Trp Asn
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Tyr His Gly Ser Tyr Asp Val Lys Pro Thr Gly Ser Ala Ser Ser
    2840                2845                2850

Leu Val Asn Gly Val Val Arg Leu Leu Ser Lys Pro Trp Asp Thr
    2855                2860                2865

Ile Thr Asn Val Thr Thr Met Ala Met Thr Asp Thr Thr Pro Phe
    2870                2875                2880

Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Lys Ala Pro
    2885                2890                2895

Glu Pro Pro Glu Gly Val Lys Tyr Val Leu Asn Glu Thr Thr Asn
    2900                2905                2910

Trp Leu Trp Ala Phe Leu Ala Arg Glu Lys Arg Pro Arg Met Cys
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Ser Arg Glu Glu Phe Ile Arg Lys Val Asn Ser Asn Ala Ala Leu
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Gly Ala Met Phe Glu Glu Gln Asn Gln Trp Arg Ser Ala Arg Glu
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Ala Val Glu Asp Pro Lys Phe Trp Glu Met Val Asp Glu Glu Arg
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Glu Ala His Leu Arg Gly Glu Cys His Thr Cys Ile Tyr Asn Met
    2975                2980                2985

Met Gly Lys Arg Glu Lys Lys Pro Gly Glu Phe Gly Lys Ala Lys
    2990                2995                3000

Gly Ser Arg Ala Ile Trp Phe Met Trp Leu Gly Ala Arg Phe Leu
    3005                3010                3015

Glu Phe Glu Ala Leu Gly Phe Leu Asn Glu Asp His Trp Leu Gly
    3020                3025                3030

Arg Lys Asn Ser Gly Gly Gly Val Glu Gly Leu Gly Leu Gln Lys
    3035                3040                3045

Leu Gly Tyr Ile Leu Arg Glu Val Gly Thr Arg Pro Gly Gly Lys
    3050                3055                3060

Ile Tyr Ala Asp Asp Thr Ala Gly Trp Asp Thr Arg Ile Thr Arg
    3065                3070                3075

Ala Asp Leu Glu Asn Glu Ala Lys Val Leu Glu Leu Leu Asp Gly
    3080                3085                3090

Glu His Arg Arg Leu Ala Arg Ala Ile Ile Glu Leu Thr Tyr Arg
    3095                3100                3105

His Lys Val Val Lys Val Met Arg Pro Ala Ala Asp Gly Arg Thr
    3110                3115                3120

Val Met Asp Val Ile Ser Arg Glu Asp Gln Arg Gly Ser Gly Gln
    3125                3130                3135

Val Val Thr Tyr Ala Leu Asn Thr Phe Thr Asn Leu Ala Val Gln
    3140                3145                3150

Leu Val Arg Met Met Glu Gly Glu Gly Val Ile Gly Pro Asp Asp
    3155                3160                3165

Val Glu Lys Leu Thr Lys Gly Lys Gly Pro Lys Val Arg Thr Trp
    3170                3175                3180

Leu Phe Glu Asn Gly Glu Glu Arg Leu Ser Arg Met Ala Val Ser
    3185                3190                3195

Gly Asp Asp Cys Val Val Lys Pro Leu Asp Asp Arg Phe Ala Thr
    3200                3205                3210
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Ser Leu  His Phe Leu Asn Ala  Met Ser Lys Val Arg  Lys Asp Ile
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Gln Glu  Trp Lys Pro Ser Thr  Gly Trp Tyr Asp Trp  Gln Gln Val
    3230                 3235                 3240

Pro Phe  Cys Ser Asn His Phe  Thr Glu Leu Ile Met  Lys Asp Gly
    3245                 3250                 3255

Arg Thr  Leu Val Val Pro Cys  Arg Gly Gln Asp Glu  Leu Val Gly
    3260                 3265                 3270

Arg Ala  Arg Ile Ser Pro Gly  Ala Gly Trp Asn Val  Arg Asp Thr
    3275                 3280                 3285

Ala Cys  Leu Ala Lys Ser Tyr  Ala Gln Met Trp Leu  Leu Leu Tyr
    3290                 3295                 3300

Phe His  Arg Arg Asp Leu Arg  Leu Met Ala Asn Ala  Ile Cys Ser
    3305                 3310                 3315

Ala Val  Pro Val Asn Trp Val  Pro Thr Gly Arg Thr  Thr Trp Ser
    3320                 3325                 3330

Ile His  Ala Gly Gly Glu Trp  Met Thr Thr Glu Asp  Met Leu Glu
    3335                 3340                 3345

Val Trp  Asn Arg Val Trp Ile  Glu Glu Asn Glu Trp  Met Glu Asp
    3350                 3355                 3360

Lys Thr  Pro Val Glu Lys Trp  Ser Asp Val Pro Tyr  Ser Gly Lys
    3365                 3370                 3375

Arg Glu  Asp Ile Trp Cys Gly  Ser Leu Ile Gly Thr  Arg Ala Arg
    3380                 3385                 3390

Ala Thr  Trp Ala Glu Asn Ile  Gln Val Ala Ile Asn  Gln Val Arg
    3395                 3400                 3405

Ala Ile  Ile Gly Asp Glu Lys  Tyr Val Asp Tyr Met  Ser Ser Leu
    3410                 3415                 3420

Lys Arg  Tyr Glu Asp Thr Thr  Leu Val Glu Asp Thr  Val Leu
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<223> OTHER INFORMATION: Synthetic polypeptide

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Ala Met Leu Ser Leu Ile Asp Gly Lys Gly Pro Ile Arg Phe Val Leu
        35                  40                  45

Ala Leu Leu Ala Phe Phe Arg Phe Thr Ala Ile Ala Pro Thr Arg Ala
    50                  55                  60

Val Leu Asp Arg Trp Arg Gly Val Asn Lys Gln Thr Ala Met Lys His
65                  70                  75                  80

Leu Leu Ser Phe Lys Lys Glu Leu Gly Thr Leu Thr Ser Ala Ile Asn
                85                  90                  95

Arg Arg Ser Ser Lys Gln Lys Lys Arg Gly Gly Lys Thr Ser Val Gly
            100                 105                 110

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

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

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

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

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

Asn Thr Thr Ser Thr Trp Val Val Tyr Gly Thr Cys His His Lys Lys
        195                 200                 205
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Gly Glu Ala Arg Arg Ser Arg Arg Ala Val Thr Leu Pro Ser His Ser
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Thr Arg Lys Leu Gln Thr Arg Ser Gln Thr Trp Leu Glu Ser Arg Glu
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Tyr Thr Lys His Leu Ile Arg Val Glu Asn Trp Ile Phe Arg Asn Pro
                245                 250                 255

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gly Val Ser Tyr Ser Leu Cys Thr Ala Ala Phe Thr Phe Thr Lys Ile
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Pro Ala Glu Thr Leu His Gly Thr Val Thr Val Glu Val Gln Tyr Ala
    610                 615                 620

Gly Thr Asp Gly Pro Cys Lys Val Pro Ala Gln Met Ala Val Asp Met
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Gln Thr Leu Thr Pro Val Gly Arg Leu Ile Thr Ala Asn Pro Val Ile
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Thr Glu Ser Thr Glu Asn Ser Lys Met Met Leu Glu Leu Asp Pro Pro
            660                 665                 670

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

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

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

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

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

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

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

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

Ile Asp Ile Ser Arg Gln Glu Leu Arg Cys Gly Ser Gly Val Phe Ile
                805                 810                 815

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

Thr Pro Gln Gly Leu Ala Lys Ile Ile Gln Lys Ala His Lys Glu Gly
        835                 840                 845

Val Cys Gly Leu Arg Ser Val Ser Arg Leu Glu His Gln Met Trp Glu
    850                 855                 860

Ala Val Lys Asp Glu Leu Asn Thr Leu Leu Lys Glu Asn Gly Val Asp
865                 870                 875                 880

Leu Ser Val Val Val Glu Lys Gln Glu Gly Met Tyr Lys Ser Ala Pro
                885                 890                 895

Lys Arg Leu Thr Ala Thr Thr Glu Lys Leu Glu Ile Gly Trp Lys Ala
            900                 905                 910

Trp Gly Lys Ser Ile Leu Phe Ala Pro Glu Leu Ala Asn Asn Thr Phe
        915                 920                 925

Val Val Asp Gly Pro Glu Thr Lys Glu Cys Pro Thr Gln Asn Arg Ala
    930                 935                 940

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

Arg Met Phe Leu Lys Val Arg Glu Ser Asn Thr Thr Glu Cys Asp Ser
                965                 970                 975

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

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

Arg Ala  Val Leu Gly Glu Val  Lys Ser Cys Thr Trp  Pro Glu Thr
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His Thr  Leu Trp Gly Asp Gly  Ile Leu Glu Ser Asp  Leu Ile Ile
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Pro Val  Thr Leu Ala Gly Pro  Arg Ser Asn His Asn  Arg Arg Pro
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Glu Ile  Asp Phe Asp Tyr Cys  Pro Gly Thr Thr Val  Thr Leu Ser
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Glu Ser  Cys Gly His Arg Gly  Pro Ala Thr Arg Thr  Thr Thr Glu
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Ser Gly  Lys Leu Ile Thr Asp  Trp Cys Cys Arg Ser  Cys Thr Leu
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Pro Pro  Leu Arg Tyr Gln Thr  Asp Ser Gly Cys Trp  Tyr Gly Met
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Glu Ile  Arg Pro Gln Arg His  Asp Glu Lys Thr Leu  Val Gln Ser
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Gln Val  Asn Ala Tyr Asn Ala  Asp Met Ile Asp Pro  Phe Gln Leu
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Gly Leu  Leu Val Val Phe Leu  Ala Thr Gln Glu Val  Leu Arg Lys
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Arg Trp  Thr Ala Lys Ile Ser  Met Pro Ala Ile Leu  Ile Ala Leu
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Leu Val  Leu Val Phe Gly Gly  Ile Thr Tyr Thr Asp  Val Leu Arg
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Tyr Val  Ile Leu Val Gly Ala  Ala Phe Ala Glu Ser  Asn Ser Gly
    1205                 1210                 1215

Gly Asp  Val Val His Leu Ala  Leu Met Ala Thr Phe  Lys Ile Gln
    1220                 1225                 1230

Pro Val  Phe Met Val Ala Ser  Phe Leu Lys Ala Arg  Trp Thr Asn
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Gln Glu  Asn Ile Leu Leu Met  Leu Ala Ala Val Phe  Phe Gln Met
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Ala Tyr  Tyr Asp Ala Arg Gln  Ile Leu Leu Trp Glu  Ile Pro Asp
    1265                 1270                 1275

Val Leu  Asn Ser Leu Ala Val  Ala Trp Met Ile Leu  Arg Ala Ile
    1280                 1285                 1290

Thr Phe  Thr Thr Thr Ser Asn  Val Val Val Pro Leu  Leu Ala Leu
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Leu Thr  Pro Gly Leu Arg Cys  Leu Asn Leu Asp Val  Tyr Arg Ile
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Leu Leu  Leu Met Val Gly Ile  Gly Ser Leu Ile Arg  Glu Lys Arg
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Ser Ala  Ala Ala Lys Lys Lys  Gly Ala Ser Leu Leu  Cys Leu Ala
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Leu Ala  Ser Thr Gly Leu Phe  Asn Pro Met Ile Leu  Ala Ala Gly
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Leu Ile  Ala Cys Asp Pro Asn  Arg Lys Arg Gly Trp  Pro Ala Thr
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Glu Val  Met Thr Ala Val Gly  Leu Met Phe Ala Ile  Val Gly Gly
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Leu Ala  Glu Leu Asp Ile Asp  Ser Met Ala Ile Pro  Met Thr Ile
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Ala Gly  Leu Met Phe Ala Ala  Phe Val Ile Ser Gly  Lys Ser Thr
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Asp Met  Trp Ile Glu Arg Thr  Ala Asp Ile Ser Trp  Glu Ser Asp
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Thr Pro  Trp Ala Ile Leu Pro  Ser Val Val Gly Phe  Trp Ile Thr
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Leu Gln  Tyr Thr Lys Arg Gly  Gly Val Leu Trp Asp  Thr Pro Ser
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Pro Lys  Glu Tyr Lys Lys Gly  Asp Thr Thr Thr Gly  Val Tyr Arg
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Val Met  Val Glu Gly Val Phe  His Thr Leu Trp His  Thr Thr Lys
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Gly Ala  Ala Leu Met Ser Gly  Glu Gly Arg Leu Asp  Pro Tyr Trp
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Gly Ser  Val Lys Glu Asp Arg  Leu Cys Tyr Gly Gly  Pro Trp Lys
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Leu Gln  His Lys Trp Asn Gly  Gln Asp Glu Val Gln  Met Ile Val
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Val Glu  Pro Gly Arg Asn Val  Lys Asn Val Gln Thr  Lys Pro Gly
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Phe Pro  Thr Gly Thr Ser Gly  Ser Pro Ile Val Asp  Lys Asn Gly
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Asp Val  Ile Gly Leu Tyr Gly  Asn Gly Val Ile Met  Pro Asn Gly
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Ser Tyr  Ile Ser Ala Ile Val  Gln Gly Glu Arg Met  Asp Glu Pro
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Ile Pro  Ala Gly Phe Glu Pro  Glu Met Leu Arg Lys  Lys Gln Ile
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Thr Val  Leu Asp Leu His Pro  Gly Ala Gly Lys Thr  Arg Arg Ile
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Leu Pro  Gln Ile Ile Lys Glu  Ala Ile Asn Arg Arg  Leu Arg Thr
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Ala Val  Leu Ala Pro Thr Arg  Val Val Ala Ala Glu  Met Ala Glu
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Ala Leu  Arg Gly Leu Pro Ile  Arg Tyr Gln Thr Ser  Ala Val Pro
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Thr Leu  Thr His Arg Leu Met  Ser Pro His Arg Val  Pro Asn Tyr
    1775                 1780                 1785

Asn Leu  Phe Val Met Asp Glu  Ala His Phe Thr Asp  Pro Ala Ser
    1790                 1795                 1800

Ile Ala  Ala Arg Gly Tyr Ile  Ser Thr Lys Val Glu  Leu Gly Glu
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Pro Phe  Pro Glu Ser Asn Ser  Pro Ile Ser Asp Leu  Gln Thr Glu
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Ile Pro  Asp Arg Ala Trp Asn  Ser Gly Tyr Glu Trp  Ile Thr Glu
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Tyr Thr  Gly Lys Thr Val Trp  Phe Val Pro Ser Val  Lys Met Gly
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Asn Glu  Ile Ala Leu Cys Leu  Gln Arg Ala Gly Lys  Lys Val Val
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Gln Leu  Asn Arg Lys Ser Tyr  Glu Thr Glu Tyr Pro  Lys Cys Lys
    1895                1900                1905

Asn Asp  Asp Trp Asp Phe Val  Ile Thr Thr Asp Ile  Ser Glu Met
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Gly Ala  Asn Phe Lys Ala Ser  Arg Val Ile Asp Ser  Arg Lys Ser
    1925                1930                1935

Val Lys  Pro Thr Ile Ile Thr  Glu Gly Glu Gly Arg  Val Ile Leu
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Gly Glu  Pro Ser Ala Val Thr  Ala Ala Ser Ala Ala  Gln Arg Arg
    1955                1960                1965

Gly Arg  Ile Gly Arg Asn Pro  Ser Gln Val Gly Asp  Glu Tyr Cys
    1970                1975                1980

Tyr Gly  Gly His Thr Asn Glu  Asp Asp Ser Asn Phe  Ala His Trp
    1985                1990                1995

Thr Glu  Ala Arg Ile Met Leu  Asp Asn Ile Asn Met  Pro Asn Gly
    2000                2005                2010

Leu Ile  Ala Gln Phe Tyr Gln  Pro Glu Arg Glu Lys  Val Tyr Thr
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Met Asp  Gly Glu Tyr Arg Leu  Arg Gly Glu Glu Arg  Lys Asn Phe
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Leu Glu  Leu Leu Arg Thr Ala  Asp Leu Pro Val Trp  Leu Ala Tyr
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Lys Val  Ala Ala Ala Gly Val  Ser Tyr His Asp Arg  Arg Trp Cys
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Phe Asp  Gly Pro Arg Thr Asn  Thr Ile Leu Glu Asp  Asn Asn Glu
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Val Glu  Val Ile Thr Lys Leu  Gly Glu Arg Lys Ile  Leu Arg Pro
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Ala Phe  Lys Asp Phe Ala Ser  Gly Lys Arg Ser Gln  Ile Gly Leu
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Ile Glu  Val Leu Gly Lys Met  Pro Glu His Phe Met  Gly Lys Thr
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Trp Glu  Ala Leu Asp Thr Met  Tyr Val Val Ala Thr  Ala Glu Lys
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Gly Gly  Arg Ala His Arg Met  Ala Leu Glu Glu Leu  Pro Asp Ala
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Gly Val  Phe Phe Leu Leu Met  Gln Arg Lys Gly Ile  Gly Lys Ile
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Gly Leu  Gly Gly Ala Val Leu  Gly Val Ala Thr Phe  Phe Cys Trp
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Met Thr  Leu Val Ser Ala Val  Ala Ala Asn Glu Met  Gly Trp Leu
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Asp Lys  Thr Lys Ser Asp Ile  Ser Ser Leu Phe Gly  Gln Arg Ile
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Leu Thr  Pro Leu Leu Lys His  Leu Ile Thr Ser Asp  Tyr Ile Asn
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Thr Ser  Leu Thr Ser Ile Asn  Val Gln Ala Ser Ala  Leu Phe Thr
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Leu Ala  Arg Gly Phe Pro Phe  Val Asp Val Gly Val  Ser Ala Leu
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Leu Leu  Ala Ala Gly Cys Trp  Gly Gln Val Thr Leu  Thr Val Thr
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Val Thr  Ala Ala Thr Leu Leu  Phe Cys His Tyr Ala  Tyr Met Val
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Pro Gly  Trp Gln Ala Glu Ala  Met Arg Ser Ala Gln  Arg Arg Thr
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Thr Asp  Val Pro Glu Leu Glu  Arg Thr Thr Pro Ile  Met Gln Lys
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Lys Val  Gly Gln Ile Met Leu  Ile Leu Val Ser Leu  Ala Ala Val
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Val Val  Asn Pro Ser Val Lys  Thr Val Arg Glu Ala  Gly Ile Leu
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Val Trp  Asn Ala Thr Thr Ala  Ile Gly Leu Cys His  Ile Met Arg
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Thr Leu  Gly Glu Val Trp Lys  Glu Arg Leu Asn Gln  Met Thr Lys
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Gly His  Pro Val Ser Arg Gly  Thr Ala Lys Leu Arg  Trp Leu Val
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Glu Arg  Arg Phe Leu Glu Pro  Val Gly Lys Val Ile  Asp Leu Gly
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Cys Gly  Arg Gly Gly Trp Cys  Tyr Tyr Met Ala Thr  Gln Lys Arg
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Ile Tyr  Ala Asp Asp Thr Ala  Gly Trp Asp Thr Arg  Ile Thr Arg
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His Lys  Val Val Lys Val Met  Arg Pro Ala Ala Asp  Gly Arg Thr
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Val Met  Asp Val Ile Ser Arg  Glu Asp Gln Arg Gly  Ser Gly Gln
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Val Val  Thr Tyr Ala Leu Asn  Thr Phe Thr Asn Leu  Ala Val Gln
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Leu Val  Arg Met Met Glu Gly  Glu Gly Val Ile Gly  Pro Asp Asp
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Val Glu  Lys Leu Thr Lys Gly  Lys Gly Pro Lys Val  Arg Thr Trp
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Gly Asp  Asp Cys Val Val Lys  Pro Leu Asp Asp Arg  Phe Ala Thr
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Ser Leu  His Phe Leu Asn Ala  Met Ser Lys Val Arg  Lys Asp Ile
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Gln Glu  Trp Lys Pro Ser Thr  Gly Trp Tyr Asp Trp  Gln Gln Val
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Pro Phe  Cys Ser Asn His Phe  Thr Glu Leu Ile Met  Lys Asp Gly
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Arg Thr  Leu Val Val Pro Cys  Arg Gly Gln Asp Glu  Leu Val Gly
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Ala Cys  Leu Ala Lys Ser Tyr  Ala Gln Met Trp Leu  Leu Leu Tyr
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Phe His  Arg Arg Asp Leu Arg  Leu Met Ala Asn Ala  Ile Cys Ser
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Ile His  Ala Gly Gly Glu Trp  Met Thr Thr Glu Asp  Met Leu Glu
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Val Trp  Asn Arg Val Trp Ile  Glu Glu Asn Glu Trp  Met Glu Asp
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Lys Thr  Pro Val Glu Lys Trp  Ser Asp Val Pro Tyr  Ser Gly Lys
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Arg Glu  Asp Ile Trp Cys Gly  Ser Leu Ile Gly Thr  Arg Ala Arg
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Ala Ile  Ile Gly Asp Glu Lys  Tyr Val Asp Tyr Met  Ser Ser Leu
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<223> OTHER INFORMATION: Synthetic polypeptide

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35 40 45

Met Lys Tyr Arg Met Glu Gly Cys Val Asp Gly His Lys Phe Val Ile
50 55 60

Thr Gly Glu Gly Ile Gly Tyr Pro Phe Lys Gly Lys Gln Ala Ile Asn
65 70 75 80

Leu Cys Val Val Glu Gly Gly Pro Leu Pro Phe Ala Glu Asp Ile Leu
85 90 95

Ser Ala Ala Phe Met Tyr Gly Asn Arg Val Phe Thr Glu Tyr Pro Gln
100 105 110

Asp Ile Ala Asp Tyr Phe Lys Asn Ser Cys Pro Ala Gly Tyr Thr Trp
115 120 125

Asp Arg Ser Phe Leu Phe Glu Asp Gly Ala Val Cys Ile Cys Asn Ala
130 135 140

Asp Ile Thr Val Ser Val Glu Glu Asn Cys Met Tyr His Glu Ser Lys
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Phe Tyr Gly Val Asn Phe Pro Ala Asp Gly Pro Val Met Lys Lys Met
165 170 175

Thr Asp Asn Trp Glu Pro Ser Cys Glu Lys Ile Ile Pro Val Pro Lys
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Gln Gly Ile Leu Lys Gly Asp Val Ser Met Tyr Leu Leu Lys Asp
195 200 205

Gly Gly Arg Leu Arg Cys Gln Phe Asp Thr Val Tyr Lys Ala Lys Ser
210 215 220

Val Pro Arg Lys Met Pro Asp Trp His Phe Ile Gln His Lys Leu Thr
225 230 235 240

Arg Glu Asp Arg Ser Asp Ala Lys Asn Gln Lys Trp His Leu Thr Glu
245 250 255

His Ala Ile Ala Ser Gly Ser Ala Leu Pro Gly Ser Gly Ala Thr Asn
260 265 270

Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro

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Met Ser Lys Lys Pro Gly Gly Pro Gly Lys Ser Arg Ala Val Asn Met
    290                 295                 300

Leu Lys Arg Gly Met Pro Arg Val Leu Ser Leu Ile Gly Leu Lys Arg
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Ala Met Leu Ser Leu Ile Asp Gly Lys Gly Pro Ile Arg Phe Val Leu
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Ala Leu Leu Ala Phe Phe Arg Phe Thr Ala Ile Ala Pro Thr Arg Ala
            340                 345                 350

Val Leu Asp Arg Trp Arg Gly Val Asn Lys Gln Thr Ala Met Lys His
        355                 360                 365

Leu Leu Ser Phe Lys Lys Glu Leu Gly Thr Leu Thr Ser Ala Ile Asn
    370                 375                 380

Arg Arg Ser Ser Lys Gln Lys Lys Arg Gly Gly Lys Thr Gly Ile Ala
385                 390                 395                 400

Val Met Ile Gly Leu Ile Ala Ser Ala Met Ala Ala Glu Val Thr Arg
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Arg Gly Ser Ala Tyr Tyr Met Tyr Leu Asp Arg Asn Asp Ala Gly Glu
            420                 425                 430

Ala Ile Ser Phe Pro Thr Thr Leu Gly Met Asn Lys Cys Tyr Ile Gln
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Ile Met Asp Leu Gly His Met Cys Asp Ala Thr Met Ser Tyr Glu Cys
    450                 455                 460

Pro Met Leu Asp Glu Gly Val Glu Pro Asp Asp Val Asp Cys Trp Cys
465                 470                 475                 480

Asn Thr Thr Ser Thr Trp Val Val Tyr Gly Thr Cys His His Lys Lys
                485                 490                 495

Gly Glu Ala Arg Arg Ser Arg Arg Ala Val Thr Leu Pro Ser His Ser
            500                 505                 510

Thr Arg Lys Leu Gln Thr Arg Ser Gln Thr Trp Leu Glu Ser Arg Glu
        515                 520                 525

Tyr Thr Lys His Leu Ile Arg Val Glu Asn Trp Ile Phe Arg Asn Pro
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Gly Phe Ala Leu Ala Ala Ala Ala Ile Ala Trp Leu Leu Gly Ser Ser
545                 550                 555                 560

Thr Ser Gln Lys Val Ile Tyr Leu Val Met Ile Leu Leu Ile Ala Pro
                565                 570                 575

Ala Tyr Ser Ile Arg Cys Ile Gly Val Ser Asn Arg Asp Phe Val Glu
            580                 585                 590

Gly Met Ser Gly Gly Thr Trp Val Asp Ile Val Leu Glu His Gly Gly
        595                 600                 605

Cys Val Thr Val Met Ala Gln Asp Lys Pro Thr Val Asp Ile Glu Leu
    610                 615                 620

Val Thr Thr Thr Val Ser Asn Met Ala Glu Val Arg Ser Tyr Cys Tyr
625                 630                 635                 640

Glu Ala Ser Ile Ser Asp Met Ala Ser Asp Ser Arg Cys Pro Thr Gln
                645                 650                 655

Gly Glu Ala Tyr Leu Asp Lys Gln Ser Asp Thr Gln Tyr Val Cys Lys
            660                 665                 670

Arg Thr Leu Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly
        675                 680                 685

Lys Gly Ser Leu Val Thr Cys Ala Lys Phe Ala Cys Ser Lys Lys Met
    690                 695                 700
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Thr Gly Lys Ser Ile Gln Pro Glu Asn Leu Glu Tyr Arg Ile Met Leu
705                 710                 715                 720

Ser Val His Gly Ser Gln His Ser Gly Met Ile Val Asn Asp Thr Gly
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His Glu Thr Asp Glu Asn Arg Ala Lys Val Glu Ile Thr Pro Asn Ser
            740                 745                 750

Pro Arg Ala Glu Ala Thr Leu Gly Gly Phe Gly Ser Leu Gly Leu Asp
        755                 760                 765

Cys Glu Pro Arg Thr Gly Leu Asp Phe Ser Asp Leu Tyr Tyr Leu Thr
    770                 775                 780

Met Asn Asn Lys His Trp Leu Val His Lys Glu Trp Phe His Asp Ile
785                 790                 795                 800

Pro Leu Pro Trp His Ala Gly Ala Asp Thr Gly Thr Pro His Trp Asn
                805                 810                 815

Asn Lys Glu Ala Leu Val Glu Phe Lys Asp Ala His Ala Lys Arg Gln
            820                 825                 830

Thr Val Val Val Leu Gly Ser Gln Glu Gly Ala Val His Thr Ala Leu
        835                 840                 845

Ala Gly Ala Leu Glu Ala Glu Met Asp Gly Ala Lys Gly Arg Leu Ser
    850                 855                 860

Ser Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Arg Leu Lys
865                 870                 875                 880

Gly Val Ser Tyr Ser Leu Cys Thr Ala Ala Phe Thr Phe Thr Lys Ile
                885                 890                 895

Pro Ala Glu Thr Leu His Gly Thr Val Thr Val Glu Val Gln Tyr Ala
            900                 905                 910

Gly Thr Asp Gly Pro Cys Lys Val Pro Ala Gln Met Ala Val Asp Met
        915                 920                 925

Gln Thr Leu Thr Pro Val Gly Arg Leu Ile Thr Ala Asn Pro Val Ile
    930                 935                 940

Thr Glu Ser Thr Glu Asn Ser Lys Met Met Leu Glu Leu Asp Pro Pro
945                 950                 955                 960

Phe Gly Asp Ser Tyr Ile Val Ile Gly Val Gly Glu Lys Lys Ile Thr
                965                 970                 975

His His Trp His Arg Ser Gly Ser Thr Ile Gly Lys Ala Phe Glu Ala
            980                 985                 990

Thr Val Arg Gly Ala Lys Arg Met  Ala Val Leu Gly Asp  Thr Ala Trp
        995                 1000                 1005

Asp Phe  Gly Ser Val Gly Gly  Ala Leu Asn Ser Leu  Gly Lys Gly
    1010                 1015                 1020

Ile His  Gln Ile Phe Gly Ala  Ala Phe Lys Ser Leu  Phe Gly Gly
    1025                 1030                 1035

Met Ser  Trp Phe Ser Gln Ile  Leu Ile Gly Thr Leu  Leu Met Trp
    1040                 1045                 1050

Leu Gly  Leu Asn Thr Lys Asn  Gly Ser Ile Ser Leu  Met Cys Leu
    1055                 1060                 1065

Ala Leu  Gly Gly Val Leu Ile  Phe Leu Ser Thr Ala  Val Ser Ala
    1070                 1075                 1080

Asp Ser  Gly Cys Ala Ile Asp  Ile Ser Arg Gln Glu  Leu Arg Cys
    1085                 1090                 1095

Gly Ser  Gly Val Phe Ile His  Asn Asp Val Glu Ala  Trp Met Asp
    1100                 1105                 1110
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Arg Tyr  Lys Tyr Tyr Pro Glu  Thr Pro Gln Gly Leu  Ala Lys Ile
    1115                 1120                 1125

Ile Gln  Lys Ala His Lys Glu  Gly Val Cys Gly Leu  Arg Ser Val
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Ser Arg  Leu Glu His Gln Met  Trp Glu Ala Val Lys  Asp Glu Leu
    1145                 1150                 1155

Asn Thr  Leu Leu Lys Glu Asn  Gly Val Asp Leu Ser  Val Val Val
    1160                 1165                 1170

Glu Lys  Gln Glu Gly Met Tyr  Lys Ser Ala Pro Lys  Arg Leu Thr
    1175                 1180                 1185

Ala Thr  Thr Glu Lys Leu Glu  Ile Gly Trp Lys Ala  Trp Gly Lys
    1190                 1195                 1200

Ser Ile  Leu Phe Ala Pro Glu  Leu Ala Asn Asn Thr  Phe Val Val
    1205                 1210                 1215

Asp Gly  Pro Glu Thr Lys Glu  Cys Pro Thr Gln Asn  Arg Ala Trp
    1220                 1225                 1230

Asn Ser  Leu Glu Val Glu Asp  Phe Gly Phe Gly Leu  Thr Ser Thr
    1235                 1240                 1245

Arg Met  Phe Leu Lys Val Arg  Glu Ser Asn Thr Thr  Glu Cys Asp
    1250                 1255                 1260

Ser Lys  Ile Ile Gly Thr Ala  Val Lys Asn Asn Leu  Ala Ile His
    1265                 1270                 1275

Ser Asp  Leu Ser Tyr Trp Ile  Glu Ser Arg Leu Asn  Asp Thr Trp
    1280                 1285                 1290

Lys Leu  Glu Arg Ala Val Leu  Gly Glu Val Lys Ser  Cys Thr Trp
    1295                 1300                 1305

Pro Glu  Thr His Thr Leu Trp  Gly Asp Gly Ile Leu  Glu Ser Asp
    1310                 1315                 1320

Leu Ile  Ile Pro Val Thr Leu  Ala Gly Pro Arg Ser  Asn His Asn
    1325                 1330                 1335

Arg Arg  Pro Gly Tyr Lys Thr  Gln Asn Gln Gly Pro  Trp Asp Glu
    1340                 1345                 1350

Gly Arg  Val Glu Ile Asp Phe  Asp Tyr Cys Pro Gly  Thr Thr Val
    1355                 1360                 1365

Thr Leu  Ser Glu Ser Cys Gly  His Arg Gly Pro Ala  Thr Arg Thr
    1370                 1375                 1380

Thr Thr  Glu Ser Gly Lys Leu  Ile Thr Asp Trp Cys  Cys Arg Ser
    1385                 1390                 1395

Cys Thr  Leu Pro Pro Leu Arg  Tyr Gln Thr Asp Ser  Gly Cys Trp
    1400                 1405                 1410

Tyr Gly  Met Glu Ile Arg Pro  Gln Arg His Asp Glu  Lys Thr Leu
    1415                 1420                 1425

Val Gln  Ser Gln Val Asn Ala  Tyr Asn Ala Asp Met  Ile Asp Pro
    1430                 1435                 1440

Phe Gln  Leu Gly Leu Leu Val  Val Phe Leu Ala Thr  Gln Glu Val
    1445                 1450                 1455

Leu Arg  Lys Arg Trp Thr Ala  Lys Ile Ser Met Pro  Ala Ile Leu
    1460                 1465                 1470

Ile Ala  Leu Leu Val Leu Val  Phe Gly Gly Ile Thr  Tyr Thr Asp
    1475                 1480                 1485

Val Leu  Arg Tyr Val Ile Leu  Val Gly Ala Ala Phe  Ala Glu Ser
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Asn Ser  Gly Gly Asp Val Val  His Leu Ala Leu Met  Ala Thr Phe
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Lys Ile  Gln Pro Val Phe Met  Val Ala Ser Phe Leu  Lys Ala Arg
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Trp Thr  Asn Gln Glu Asn Ile  Leu Leu Met Leu Ala  Ala Val Phe
    1535                1540                1545

Phe Gln  Met Ala Tyr Tyr Asp  Ala Arg Gln Ile Leu  Leu Trp Glu
    1550                1555                1560

Ile Pro  Asp Val Leu Asn Ser  Leu Ala Val Ala Trp  Met Ile Leu
    1565                1570                1575

Arg Ala  Ile Thr Phe Thr Thr  Thr Ser Asn Val Val  Val Pro Leu
    1580                1585                1590

Leu Ala  Leu Leu Thr Pro Gly  Leu Arg Cys Leu Asn  Leu Asp Val
    1595                1600                1605

Tyr Arg  Ile Leu Leu Leu Met  Val Gly Ile Gly Ser  Leu Ile Arg
    1610                1615                1620

Glu Lys  Arg Ser Ala Ala Ala  Lys Lys Lys Gly Ala  Ser Leu Leu
    1625                1630                1635

Cys Leu  Ala Leu Ala Ser Thr  Gly Leu Phe Asn Pro  Met Ile Leu
    1640                1645                1650

Ala Ala  Gly Leu Ile Ala Cys  Asp Pro Asn Arg Lys  Arg Gly Trp
    1655                1660                1665

Pro Ala  Thr Glu Val Met Thr  Ala Val Gly Leu Met  Phe Ala Ile
    1670                1675                1680

Val Gly  Gly Leu Ala Glu Leu  Asp Ile Asp Ser Met  Ala Ile Pro
    1685                1690                1695

Met Thr  Ile Ala Gly Leu Met  Phe Ala Ala Phe Val  Ile Ser Gly
    1700                1705                1710

Lys Ser  Thr Asp Met Trp Ile  Glu Arg Thr Ala Asp  Ile Ser Trp
    1715                1720                1725

Glu Ser  Asp Ala Glu Ile Thr  Gly Ser Ser Glu Arg  Val Asp Val
    1730                1735                1740

Arg Leu  Asp Asp Asp Gly Asn  Phe Gln Leu Met Asn  Asp Pro Gly
    1745                1750                1755

Ala Pro  Trp Lys Ile Trp Met  Leu Arg Met Val Cys  Leu Ala Ile
    1760                1765                1770

Ser Ala  Tyr Thr Pro Trp Ala  Ile Leu Pro Ser Val  Val Gly Phe
    1775                1780                1785

Trp Ile  Thr Leu Gln Tyr Thr  Lys Arg Gly Gly Val  Leu Trp Asp
    1790                1795                1800

Thr Pro  Ser Pro Lys Glu Tyr  Lys Lys Gly Asp Thr  Thr Thr Gly
    1805                1810                1815

Val Tyr  Arg Ile Met Thr Arg  Gly Leu Leu Gly Ser  Tyr Gln Ala
    1820                1825                1830

Gly Ala  Gly Val Met Val Glu  Gly Val Phe His Thr  Leu Trp His
    1835                1840                1845

Thr Thr  Lys Gly Ala Ala Leu  Met Ser Gly Glu Gly  Arg Leu Asp
    1850                1855                1860

Pro Tyr  Trp Gly Ser Val Lys  Glu Asp Arg Leu Cys  Tyr Gly Gly
    1865                1870                1875

Pro Trp  Lys Leu Gln His Lys  Trp Asn Gly Gln Asp  Glu Val Gln
    1880                1885                1890

Met Ile  Val Val Glu Pro Gly  Arg Asn Val Lys Asn  Val Gln Thr
    1895                1900                1905
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Lys Pro  Gly Val Phe Lys Thr  Pro Glu Gly Glu Ile  Gly Ala Val
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Thr Leu  Asp Phe Pro Thr Gly  Thr Ser Gly Ser Pro  Ile Val Asp
    1925                 1930                 1935

Lys Asn  Gly Asp Val Ile Gly  Leu Tyr Gly Asn Gly  Val Ile Met
    1940                 1945                 1950

Pro Asn  Gly Ser Tyr Ile Ser  Ala Ile Val Gln Gly  Glu Arg Met
    1955                 1960                 1965

Asp Glu  Pro Ile Pro Ala Gly  Phe Glu Pro Glu Met  Leu Arg Lys
    1970                 1975                 1980

Lys Gln  Ile Thr Val Leu Asp  Leu His Pro Gly Ala  Gly Lys Thr
    1985                 1990                 1995

Arg Arg  Ile Leu Pro Gln Ile  Ile Lys Glu Ala Ile  Asn Arg Arg
    2000                 2005                 2010

Leu Arg  Thr Ala Val Leu Ala  Pro Thr Arg Val Val  Ala Ala Glu
    2015                 2020                 2025

Met Ala  Glu Ala Leu Arg Gly  Leu Pro Ile Arg Tyr  Gln Thr Ser
    2030                 2035                 2040

Ala Val  Pro Arg Glu His Asn  Gly Asn Glu Ile Val  Asp Val Met
    2045                 2050                 2055

Cys His  Ala Thr Leu Thr His  Arg Leu Met Ser Pro  His Arg Val
    2060                 2065                 2070

Pro Asn  Tyr Asn Leu Phe Val  Met Asp Glu Ala His  Phe Thr Asp
    2075                 2080                 2085

Pro Ala  Ser Ile Ala Ala Arg  Gly Tyr Ile Ser Thr  Lys Val Glu
    2090                 2095                 2100

Leu Gly  Glu Ala Ala Ala Ile  Phe Met Thr Ala Thr  Pro Pro Gly
    2105                 2110                 2115

Thr Ser  Asp Pro Phe Pro Glu  Ser Asn Ser Pro Ile  Ser Asp Leu
    2120                 2125                 2130

Gln Thr  Glu Ile Pro Asp Arg  Ala Trp Asn Ser Gly  Tyr Glu Trp
    2135                 2140                 2145

Ile Thr  Glu Tyr Thr Gly Lys  Thr Val Trp Phe Val  Pro Ser Val
    2150                 2155                 2160

Lys Met  Gly Asn Glu Ile Ala  Leu Cys Leu Gln Arg  Ala Gly Lys
    2165                 2170                 2175

Lys Val  Val Gln Leu Asn Arg  Lys Ser Tyr Glu Thr  Glu Tyr Pro
    2180                 2185                 2190

Lys Cys  Lys Asn Asp Asp Trp  Asp Phe Val Ile Thr  Thr Asp Ile
    2195                 2200                 2205

Ser Glu  Met Gly Ala Asn Phe  Lys Ala Ser Arg Val  Ile Asp Ser
    2210                 2215                 2220

Arg Lys  Ser Val Lys Pro Thr  Ile Ile Thr Glu Gly  Glu Gly Arg
    2225                 2230                 2235

Val Ile  Leu Gly Glu Pro Ser  Ala Val Thr Ala Ala  Ser Ala Ala
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Gln Arg  Arg Gly Arg Ile Gly  Arg Asn Pro Ser Gln  Val Gly Asp
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Glu Tyr  Cys Tyr Gly Gly His  Thr Asn Glu Asp Asp  Ser Asn Phe
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Ala His  Trp Thr Glu Ala Arg  Ile Met Leu Asp Asn  Ile Asn Met
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Pro Asn  Gly Leu Ile Ala Gln  Phe Tyr Gln Pro Glu  Arg Glu Lys
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Lys Asn  Phe Leu Glu Leu Leu  Arg Thr Ala Asp Leu  Pro Val Trp
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Leu Ala  Tyr Lys Val Ala Ala  Ala Gly Val Ser Tyr  His Asp Arg
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Arg Trp  Cys Phe Asp Gly Pro  Arg Thr Asn Thr Ile  Leu Glu Asp
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Asn Asn  Glu Val Glu Val Ile  Thr Lys Leu Gly Glu  Arg Lys Ile
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Leu Arg  Pro Arg Trp Ile Asp  Ala Arg Val Tyr Ser  Asp His Gln
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Ala Leu  Lys Ala Phe Lys Asp  Phe Ala Ser Gly Lys  Arg Ser Gln
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Ile Gly  Leu Ile Glu Val Leu  Gly Lys Met Pro Glu  His Phe Met
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Gly Lys  Thr Trp Glu Ala Leu  Asp Thr Met Tyr Val  Val Ala Thr
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Ala Glu  Lys Gly Gly Arg Ala  His Arg Met Ala Leu  Glu Glu Leu
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Pro Asp  Ala Leu Gln Thr Ile  Ala Leu Ile Ala Leu  Leu Ser Val
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Met Thr  Met Gly Val Phe Phe  Leu Leu Met Gln Arg  Lys Gly Ile
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Gly Lys  Ile Gly Leu Gly Gly  Ala Val Leu Gly Val  Ala Thr Phe
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Phe Cys  Trp Met Ala Glu Val  Pro Gly Thr Lys Ile  Ala Gly Met
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Leu Leu  Leu Ser Leu Leu Leu  Met Ile Val Leu Ile  Pro Glu Pro
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Glu Lys  Gln Arg Ser Gln Thr  Asp Asn Gln Leu Ala  Val Phe Leu
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Ile Cys  Val Met Thr Leu Val  Ser Ala Val Ala Ala  Asn Glu Met
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Gly Trp  Leu Asp Lys Thr Lys  Ser Asp Ile Ser Ser  Leu Phe Gly
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Gln Arg  Ile Glu Val Lys Glu  Asn Phe Ser Met Gly  Glu Phe Leu
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Leu Asp  Leu Arg Pro Ala Thr  Ala Trp Ser Leu Tyr  Ala Val Thr
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Thr Ala  Val Leu Thr Pro Leu  Leu Lys His Leu Ile  Thr Ser Asp
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Tyr Ile  Asn Thr Ser Leu Thr  Ser Ile Asn Val Gln  Ala Ser Ala
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Leu Phe  Thr Leu Ala Arg Gly  Phe Pro Phe Val Asp  Val Gly Val
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Ser Ala  Leu Leu Leu Ala Ala  Gly Cys Trp Gly Gln  Val Thr Leu
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Tyr Met  Val Pro Gly Trp Gln  Ala Glu Ala Met Arg  Ser Ala Gln
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Met Gln  Lys Lys Val Gly Gln  Ile Met Leu Ile Leu  Val Ser Leu
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Gly Ile  Leu Ile Thr Ala Ala  Ala Val Thr Leu Trp  Glu Asn Gly
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Gly His  Glu Glu Pro Gln Leu  Val Gln Ser Tyr Gly  Trp Asn Ile
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Glu Asp  Trp Leu His Arg Gly  Pro Arg Glu Phe Cys  Val Lys Val
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Tyr Asn  Met Met Gly Lys Arg  Glu Lys Lys Pro Gly  Glu Phe Gly
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Lys Ala  Lys Gly Ser Arg Ala  Ile Trp Phe Met Trp  Leu Gly Ala
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Leu Asp  Gly Glu His Arg Arg  Leu Ala Arg Ala Ile  Ile Glu Leu
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Pro Asp  Asp Val Glu Lys Leu  Thr Lys Gly Lys Gly  Pro Lys Val
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Arg Thr  Trp Leu Phe Glu Asn  Gly Glu Glu Arg Leu  Ser Arg Met
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Phe Ala  Thr Ser Leu His Phe  Leu Asn Ala Met Ser  Lys Val Arg
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Lys Asp  Ile Gln Glu Trp Lys  Pro Ser Thr Gly Trp  Tyr Asp Trp
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Gln Gln  Val Pro Phe Cys Ser  Asn His Phe Thr Glu  Leu Ile Met
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Lys Asp  Gly Arg Thr Leu Val  Val Pro Cys Arg Gly  Gln Asp Glu
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Leu Val  Gly Arg Ala Arg Ile  Ser Pro Gly Ala Gly  Trp Asn Val
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Arg Asp  Thr Ala Cys Leu Ala  Lys Ser Tyr Ala Gln  Met Trp Leu
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Leu Leu  Tyr Phe His Arg Arg  Asp Leu Arg Leu Met  Ala Asn Ala
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Ile Cys  Ser Ala Val Pro Val  Asn Trp Val Pro Thr  Gly Arg Thr
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Thr Trp  Ser Ile His Ala Gly  Gly Glu Trp Met Thr  Thr Glu Asp
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Met Glu  Asp Lys Thr Pro Val  Glu Lys Trp Ser Asp  Val Pro Tyr
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Ser Gly  Lys Arg Glu Asp Ile  Trp Cys Gly Ser Leu  Ile Gly Thr
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Arg Ala  Arg Ala Thr Trp Ala  Glu Asn Ile Gln Val  Ala Ile Asn
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Gln Val  Arg Ala Ile Ile Gly  Asp Glu Lys Tyr Val  Asp Tyr Met
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 12

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Leu Lys Arg Gly Met Pro Arg Val Leu Ser Leu Ile Gly Leu Lys Arg
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Ala Met Leu Met Ala Gln Ser Lys His Gly Leu Thr Lys Glu Met Thr
        35                  40                  45

Met Lys Tyr Arg Met Glu Gly Cys Val Asp Gly His Lys Phe Val Ile
    50                  55                  60

Thr Gly Glu Gly Ile Gly Tyr Pro Phe Lys Gly Lys Gln Ala Ile Asn
65                  70                  75                  80

Leu Cys Val Val Glu Gly Gly Pro Leu Pro Phe Ala Glu Asp Ile Leu
                85                  90                  95

Ser Ala Ala Phe Met Tyr Gly Asn Arg Val Phe Thr Glu Tyr Pro Gln
            100                 105                 110

Asp Ile Val Asp Tyr Phe Lys Asn Ser Cys Pro Ala Gly Tyr Thr Trp
        115                 120                 125

Asp Arg Ser Phe Leu Phe Glu Asp Gly Ala Val Cys Ile Cys Asn Ala
    130                 135                 140

Asp Ile Thr Val Ser Val Glu Glu Asn Cys Met Tyr His Glu Ser Lys
145                 150                 155                 160

Phe Tyr Gly Val Asn Phe Pro Ala Asp Gly Pro Val Met Lys Lys Met
                165                 170                 175

Thr Asp Asn Trp Glu Pro Ser Cys Glu Lys Ile Ile Pro Val Pro Lys
            180                 185                 190

Gln Gly Ile Leu Lys Gly Asp Val Ser Met Tyr Leu Leu Leu Lys Asp
        195                 200                 205

Gly Gly Arg Leu Arg Cys Gln Phe Asp Thr Val Tyr Lys Ala Lys Ser
    210                 215                 220

Val Pro Arg Lys Met Pro Asp Trp His Phe Ile Gln His Lys Leu Thr
225                 230                 235                 240

Arg Glu Asp Arg Ser Asp Ala Lys Asn Gln Lys Trp His Leu Thr Glu
                245                 250                 255

His Ala Ile Ala Ser Gly Ser Ala Leu Pro Gly Ser Gly Ala Thr Asn
            260                 265                 270

Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro
        275                 280                 285

Met Ser Lys Lys Pro Gly Gly Pro Gly Lys Ser Arg Ala Val Asn Met
    290                 295                 300

Leu Lys Arg Gly Met Pro Arg Val Leu Ser Leu Ile Gly Leu Lys Arg
305                 310                 315                 320

Ala Met Leu Ser Leu Ile Asp Gly Lys Gly Pro Ile Arg Phe Val Leu
                325                 330                 335

Ala Leu Leu Ala Phe Phe Arg Phe Thr Ala Ile Ala Pro Thr Arg Ala
            340                 345                 350

Val Leu Asp Arg Trp Arg Gly Val Asn Lys Gln Thr Ala Met Lys His
        355                 360                 365

Leu Leu Ser Phe Lys Lys Glu Leu Gly Thr Leu Thr Ser Ala Ile Asn
    370                 375                 380

Arg Arg Ser Ser Lys Gln Lys Lys Arg Gly Gly Lys Thr Gly Ile Ala
385                 390                 395                 400

Val Met Ile Gly Leu Ile Ala Ser Ala Met Ala Ala Glu Val Thr Arg
                405                 410                 415

Arg Gly Ser Ala Tyr Tyr Met Tyr Leu Asp Arg Asn Asp Ala Gly Glu
            420                 425                 430

Ala Ile Ser Phe Pro Thr Thr Leu Gly Met Asn Lys Cys Tyr Ile Gln
        435                 440                 445
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Ile Met Asp Leu Gly His Met Cys Asp Ala Thr Met Ser Tyr Glu Cys
    450                 455                 460

Pro Met Leu Asp Glu Gly Val Glu Pro Asp Asp Val Asp Cys Trp Cys
465                 470                 475                 480

Asn Thr Thr Ser Thr Trp Val Val Tyr Gly Thr Cys His His Lys Lys
                485                 490                 495

Gly Glu Ala Arg Arg Ser Arg Arg Ala Val Thr Leu Pro Ser His Ser
            500                 505                 510

Thr Arg Lys Leu Gln Thr Arg Ser Gln Thr Trp Leu Glu Ser Arg Glu
        515                 520                 525

Tyr Thr Lys His Leu Ile Arg Val Glu Asn Trp Ile Phe Arg Asn Pro
    530                 535                 540

Gly Phe Ala Leu Ala Ala Ala Ala Ile Ala Trp Leu Leu Gly Ser Ser
545                 550                 555                 560

Thr Ser Gln Lys Val Ile Tyr Leu Val Met Ile Leu Leu Ile Ala Pro
                565                 570                 575

Ala Tyr Ser Ile Arg Cys Ile Gly Val Ser Asn Arg Asp Phe Val Glu
            580                 585                 590

Gly Met Ser Gly Gly Thr Trp Val Asp Ile Val Leu Glu His Gly Gly
        595                 600                 605

Cys Val Thr Val Met Ala Gln Asp Lys Pro Thr Val Asp Ile Glu Leu
    610                 615                 620

Val Thr Thr Thr Val Ser Asn Met Ala Glu Val Arg Ser Tyr Cys Tyr
625                 630                 635                 640

Glu Ala Ser Ile Ser Asp Met Ala Ser Asp Ser Arg Cys Pro Thr Gln
                645                 650                 655

Gly Glu Ala Tyr Leu Asp Lys Gln Ser Asp Thr Gln Tyr Val Cys Lys
            660                 665                 670

Arg Thr Leu Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly
        675                 680                 685

Lys Gly Ser Leu Val Thr Cys Ala Lys Phe Ala Cys Ser Lys Lys Met
    690                 695                 700

Thr Gly Lys Ser Ile Gln Pro Glu Asn Leu Glu Tyr Arg Ile Met Leu
705                 710                 715                 720

Ser Val His Gly Ser Gln His Ser Gly Met Ile Val Asn Asp Thr Gly
                725                 730                 735

His Glu Thr Asp Glu Asn Arg Ala Lys Val Glu Ile Thr Pro Asn Ser
            740                 745                 750

Pro Arg Ala Glu Ala Thr Leu Gly Gly Phe Gly Ser Leu Gly Leu Asp
        755                 760                 765

Cys Glu Pro Arg Thr Gly Leu Asp Phe Ser Asp Leu Tyr Tyr Leu Thr
    770                 775                 780

Met Asn Asn Lys His Trp Leu Val His Lys Glu Trp Phe His Asp Ile
785                 790                 795                 800

Pro Leu Pro Trp His Ala Gly Ala Asp Thr Gly Thr Pro His Trp Asn
                805                 810                 815

Asn Lys Glu Ala Leu Val Glu Phe Lys Asp Ala His Ala Lys Arg Gln
            820                 825                 830

Thr Val Val Val Leu Gly Ser Gln Glu Gly Ala Val His Thr Ala Leu
        835                 840                 845

Ala Gly Ala Leu Glu Ala Glu Met Asp Gly Ala Lys Gly Arg Leu Ser
    850                 855                 860

Ser Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Arg Leu Lys
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865                 870                 875                 880

Gly Val Ser Tyr Ser Leu Cys Thr Ala Ala Phe Thr Phe Thr Lys Ile
                885                 890                 895

Pro Ala Glu Thr Leu His Gly Thr Val Thr Val Glu Val Gln Tyr Ala
            900                 905                 910

Gly Thr Asp Gly Pro Cys Lys Val Pro Ala Gln Met Ala Val Asp Met
        915                 920                 925

Gln Thr Leu Thr Pro Val Gly Arg Leu Ile Thr Ala Asn Pro Val Ile
    930                 935                 940

Thr Glu Ser Thr Glu Asn Ser Lys Met Met Leu Glu Leu Asp Pro Pro
945                 950                 955                 960

Phe Gly Asp Ser Tyr Ile Val Ile Gly Val Gly Glu Lys Lys Ile Thr
                965                 970                 975

His His Trp His Arg Ser Gly Ser Thr Ile Gly Lys Ala Phe Glu Ala
            980                 985                 990

Thr Val Arg Gly Ala Lys Arg Met  Ala Val Leu Gly Asp  Thr Ala Trp
        995                 1000                1005

Asp Phe  Gly Ser Val Gly Gly  Ala Leu Asn Ser Leu  Gly Lys Gly
    1010                1015                1020

Ile His  Gln Ile Phe Gly Ala  Ala Phe Lys Ser Leu  Phe Gly Gly
    1025                1030                1035

Met Ser  Trp Phe Ser Gln Ile  Leu Ile Gly Thr Leu  Leu Met Trp
    1040                1045                1050

Leu Gly  Leu Asn Thr Lys Asn  Gly Ser Ile Ser Leu  Met Cys Leu
    1055                1060                1065

Ala Leu  Gly Gly Val Leu Ile  Phe Leu Ser Thr Ala  Val Ser Ala
    1070                1075                1080

Asp Ser  Gly Cys Ala Ile Asp  Ile Ser Arg Gln Glu  Leu Arg Cys
    1085                1090                1095

Gly Ser  Gly Val Phe Ile His  Asn Asp Val Glu Ala  Trp Met Asp
    1100                1105                1110

Arg Tyr  Lys Tyr Tyr Pro Glu  Thr Pro Gln Gly Leu  Ala Lys Ile
    1115                1120                1125

Ile Gln  Lys Ala His Lys Glu  Gly Val Cys Gly Leu  Arg Ser Val
    1130                1135                1140

Ser Arg  Leu Glu His Gln Met  Trp Glu Ala Val Lys  Asp Glu Leu
    1145                1150                1155

Asn Thr  Leu Leu Lys Glu Asn  Gly Val Asp Leu Ser  Val Val Val
    1160                1165                1170

Glu Lys  Gln Glu Gly Met Tyr  Lys Ser Ala Pro Lys  Arg Leu Thr
    1175                1180                1185

Ala Thr  Thr Glu Lys Leu Glu  Ile Gly Trp Lys Ala  Trp Gly Lys
    1190                1195                1200

Ser Ile  Leu Phe Ala Pro Glu  Leu Ala Asn Asn Thr  Phe Val Val
    1205                1210                1215

Asp Gly  Pro Glu Thr Lys Glu  Cys Pro Thr Gln Asn  Arg Ala Trp
    1220                1225                1230

Asn Ser  Leu Glu Val Glu Asp  Phe Gly Phe Gly Leu  Thr Ser Thr
    1235                1240                1245

Arg Met  Phe Leu Lys Val Arg  Glu Ser Asn Thr Thr  Glu Cys Asp
    1250                1255                1260

Ser Lys  Ile Ile Gly Thr Ala  Val Lys Asn Asn Leu  Ala Ile His
    1265                1270                1275
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Ser Asp  Leu Ser Tyr Trp Ile  Glu Ser Arg Leu Asn  Asp Thr Trp
    1280                 1285                 1290

Lys Leu  Glu Arg Ala Val Leu  Gly Glu Val Lys Ser  Cys Thr Trp
    1295                 1300                 1305

Pro Glu  Thr His Thr Leu Trp  Gly Asp Gly Ile Leu  Glu Ser Asp
    1310                 1315                 1320

Leu Ile  Ile Pro Val Thr Leu  Ala Gly Pro Arg Ser  Asn His Asn
    1325                 1330                 1335

Arg Arg  Pro Gly Tyr Lys Thr  Gln Asn Gln Gly Pro  Trp Asp Glu
    1340                 1345                 1350

Gly Arg  Val Glu Ile Asp Phe  Asp Tyr Cys Pro Gly  Thr Thr Val
    1355                 1360                 1365

Thr Leu  Ser Glu Ser Cys Gly  His Arg Gly Pro Ala  Thr Arg Thr
    1370                 1375                 1380

Thr Thr  Glu Ser Gly Lys Leu  Ile Thr Asp Trp Cys  Cys Arg Ser
    1385                 1390                 1395

Cys Thr  Leu Pro Pro Leu Arg  Tyr Gln Thr Asp Ser  Gly Cys Trp
    1400                 1405                 1410

Tyr Gly  Met Glu Ile Arg Pro  Gln Arg His Asp Glu  Lys Thr Leu
    1415                 1420                 1425

Val Gln  Ser Gln Val Asn Ala  Tyr Asn Ala Asp Met  Ile Asp Pro
    1430                 1435                 1440

Phe Gln  Leu Gly Leu Leu Val  Val Phe Leu Ala Thr  Gln Glu Val
    1445                 1450                 1455

Leu Arg  Lys Arg Trp Thr Ala  Lys Ile Ser Met Pro  Ala Ile Leu
    1460                 1465                 1470

Ile Ala  Leu Leu Val Leu Val  Phe Gly Gly Ile Thr  Tyr Thr Asp
    1475                 1480                 1485

Val Leu  Arg Tyr Val Ile Leu  Val Gly Ala Ala Phe  Ala Glu Ser
    1490                 1495                 1500

Asn Ser  Gly Gly Asp Val Val  His Leu Ala Leu Met  Ala Thr Phe
    1505                 1510                 1515

Lys Ile  Gln Pro Val Phe Met  Val Ala Ser Phe Leu  Lys Ala Arg
    1520                 1525                 1530

Trp Thr  Asn Gln Glu Asn Ile  Leu Leu Met Leu Ala  Ala Val Phe
    1535                 1540                 1545

Phe Gln  Met Ala Tyr Tyr Asp  Ala Arg Gln Ile Leu  Leu Trp Glu
    1550                 1555                 1560

Ile Pro  Asp Val Leu Asn Ser  Leu Ala Val Ala Trp  Met Ile Leu
    1565                 1570                 1575

Arg Ala  Ile Thr Phe Thr Thr  Thr Ser Asn Val Val  Val Pro Leu
    1580                 1585                 1590

Leu Ala  Leu Leu Thr Pro Gly  Leu Arg Cys Leu Asn  Leu Asp Val
    1595                 1600                 1605

Tyr Arg  Ile Leu Leu Leu Met  Val Gly Ile Gly Ser  Leu Ile Arg
    1610                 1615                 1620

Glu Lys  Arg Ser Ala Ala Ala  Lys Lys Lys Gly Ala  Ser Leu Leu
    1625                 1630                 1635

Cys Leu  Ala Leu Ala Ser Thr  Gly Leu Phe Asn Pro  Met Ile Leu
    1640                 1645                 1650

Ala Ala  Gly Leu Ile Ala Cys  Asp Pro Asn Arg Lys  Arg Gly Trp
    1655                 1660                 1665
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Pro Ala  Thr Glu Val Met Thr  Ala Val Gly Leu Met  Phe Ala Ile
    1670                 1675                 1680

Val Gly  Gly Leu Ala Glu Leu  Asp Ile Asp Ser Met  Ala Ile Pro
    1685                 1690                 1695

Met Thr  Ile Ala Gly Leu Met  Phe Ala Ala Phe Val  Ile Ser Gly
    1700                 1705                 1710

Lys Ser  Thr Asp Met Trp Ile  Glu Arg Thr Ala Asp  Ile Ser Trp
    1715                 1720                 1725

Glu Ser  Asp Ala Glu Ile Thr  Gly Ser Ser Glu Arg  Val Asp Val
    1730                 1735                 1740

Arg Leu  Asp Asp Asp Gly Asn  Phe Gln Leu Met Asn  Asp Pro Gly
    1745                 1750                 1755

Ala Pro  Trp Lys Ile Trp Met  Leu Arg Met Val Cys  Leu Ala Ile
    1760                 1765                 1770

Ser Ala  Tyr Thr Pro Trp Ala  Ile Leu Pro Ser Val  Val Gly Phe
    1775                 1780                 1785

Trp Ile  Thr Leu Gln Tyr Thr  Lys Arg Gly Gly Val  Leu Trp Asp
    1790                 1795                 1800

Thr Pro  Ser Pro Lys Glu Tyr  Lys Lys Gly Asp Thr  Thr Thr Gly
    1805                 1810                 1815

Val Tyr  Arg Ile Met Thr Arg  Gly Leu Leu Gly Ser  Tyr Gln Ala
    1820                 1825                 1830

Gly Ala  Gly Val Met Val Glu  Gly Val Phe His Thr  Leu Trp His
    1835                 1840                 1845

Thr Thr  Lys Gly Ala Ala Leu  Met Ser Gly Glu Gly  Arg Leu Asp
    1850                 1855                 1860

Pro Tyr  Trp Gly Ser Val Lys  Glu Asp Arg Leu Cys  Tyr Gly Gly
    1865                 1870                 1875

Pro Trp  Lys Leu Gln His Lys  Trp Asn Gly Gln Asp  Glu Val Gln
    1880                 1885                 1890

Met Ile  Val Val Glu Pro Gly  Arg Asn Val Lys Asn  Val Gln Thr
    1895                 1900                 1905

Lys Pro  Gly Val Phe Lys Thr  Pro Glu Gly Glu Ile  Gly Ala Val
    1910                 1915                 1920

Thr Leu  Asp Phe Pro Thr Gly  Thr Ser Gly Ser Pro  Ile Val Asp
    1925                 1930                 1935

Lys Asn  Gly Asp Val Ile Gly  Leu Tyr Gly Asn Gly  Val Ile Met
    1940                 1945                 1950

Pro Asn  Gly Ser Tyr Ile Ser  Ala Ile Val Gln Gly  Glu Arg Met
    1955                 1960                 1965

Asp Glu  Pro Ile Pro Ala Gly  Phe Glu Pro Glu Met  Leu Arg Lys
    1970                 1975                 1980

Lys Gln  Ile Thr Val Leu Asp  Leu His Pro Gly Ala  Gly Lys Thr
    1985                 1990                 1995

Arg Arg  Ile Leu Pro Gln Ile  Ile Lys Glu Ala Ile  Asn Arg Arg
    2000                 2005                 2010

Leu Arg  Thr Ala Val Leu Ala  Pro Thr Arg Val Val  Ala Ala Glu
    2015                 2020                 2025

Met Ala  Glu Ala Leu Arg Gly  Leu Pro Ile Arg Tyr  Gln Thr Ser
    2030                 2035                 2040

Ala Val  Pro Arg Glu His Asn  Gly Asn Glu Ile Val  Asp Val Met
    2045                 2050                 2055

Cys His  Ala Thr Leu Thr His  Arg Leu Met Ser Pro  His Arg Val
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    2060                2065                2070

Pro Asn  Tyr Asn Leu Phe Val  Met Asp Glu Ala His  Phe Thr Asp
    2075                2080                2085

Pro Ala  Ser Ile Ala Ala Arg  Gly Tyr Ile Ser Thr  Lys Val Glu
    2090                2095                2100

Leu Gly  Glu Ala Ala Ala Ile  Phe Met Thr Ala Thr  Pro Pro Gly
    2105                2110                2115

Thr Ser  Asp Pro Phe Pro Glu  Ser Asn Ser Pro Ile  Ser Asp Leu
    2120                2125                2130

Gln Thr  Glu Ile Pro Asp Arg  Ala Trp Asn Ser Gly  Tyr Glu Trp
    2135                2140                2145

Ile Thr  Glu Tyr Thr Gly Lys  Thr Val Trp Phe Val  Pro Ser Val
    2150                2155                2160

Lys Met  Gly Asn Glu Ile Ala  Leu Cys Leu Gln Arg  Ala Gly Lys
    2165                2170                2175

Lys Val  Val Gln Leu Asn Arg  Lys Ser Tyr Glu Thr  Glu Tyr Pro
    2180                2185                2190

Lys Cys  Lys Asn Asp Asp Trp  Asp Phe Val Ile Thr  Thr Asp Ile
    2195                2200                2205

Ser Glu  Met Gly Ala Asn Phe  Lys Ala Ser Arg Val  Ile Asp Ser
    2210                2215                2220

Arg Lys  Ser Val Lys Pro Thr  Ile Ile Thr Glu Gly  Glu Gly Arg
    2225                2230                2235

Val Ile  Leu Gly Glu Pro Ser  Ala Val Thr Ala Ala  Ser Ala Ala
    2240                2245                2250

Gln Arg  Arg Gly Arg Ile Gly  Arg Asn Pro Ser Gln  Val Gly Asp
    2255                2260                2265

Glu Tyr  Cys Tyr Gly Gly His  Thr Asn Glu Asp Asp  Ser Asn Phe
    2270                2275                2280

Ala His  Trp Thr Glu Ala Arg  Ile Met Leu Asp Asn  Ile Asn Met
    2285                2290                2295

Pro Asn  Gly Leu Ile Ala Gln  Phe Tyr Gln Pro Glu  Arg Glu Lys
    2300                2305                2310

Val Tyr  Thr Met Asp Gly Glu  Tyr Arg Leu Arg Gly  Glu Glu Arg
    2315                2320                2325

Lys Asn  Phe Leu Glu Leu Leu  Arg Thr Ala Asp Leu  Pro Val Trp
    2330                2335                2340

Leu Ala  Tyr Lys Val Ala Ala  Ala Gly Val Ser Tyr  His Asp Arg
    2345                2350                2355

Arg Trp  Cys Phe Asp Gly Pro  Arg Thr Asn Thr Ile  Leu Glu Asp
    2360                2365                2370

Asn Asn  Glu Val Glu Val Ile  Thr Lys Leu Gly Glu  Arg Lys Ile
    2375                2380                2385

Leu Arg  Pro Arg Trp Ile Asp  Ala Arg Val Tyr Ser  Asp His Gln
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Ala Leu  Lys Ala Phe Lys Asp  Phe Ala Ser Gly Lys  Arg Ser Gln
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Ile Gly  Leu Ile Glu Val Leu  Gly Lys Met Pro Glu  His Phe Met
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Gly Lys  Thr Trp Glu Ala Leu  Asp Thr Met Tyr Val  Val Ala Thr
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Gly Lys  Ile Gly Leu Gly Gly  Ala Val Leu Gly Val  Ala Thr Phe
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Phe Cys  Trp Met Ala Glu Val  Pro Gly Thr Lys Ile  Ala Gly Met
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Leu Leu  Leu Ser Leu Leu Leu  Met Ile Val Leu Ile  Pro Glu Pro
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Glu Lys  Gln Arg Ser Gln Thr  Asp Asn Gln Leu Ala  Val Phe Leu
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Ile Cys  Val Met Thr Leu Val  Ser Ala Val Ala Ala  Asn Glu Met
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Gly Trp  Leu Asp Lys Thr Lys  Ser Asp Ile Ser Ser  Leu Phe Gly
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Gln Arg  Ile Glu Val Lys Glu  Asn Phe Ser Met Gly  Glu Phe Leu
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Leu Asp  Leu Arg Pro Ala Thr  Ala Trp Ser Leu Tyr  Ala Val Thr
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Thr Ala  Val Leu Thr Pro Leu  Leu Lys His Leu Ile  Thr Ser Asp
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Tyr Ile  Asn Thr Ser Leu Thr  Ser Ile Asn Val Gln  Ala Ser Ala
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Leu Phe  Thr Leu Ala Arg Gly  Phe Pro Phe Val Asp  Val Gly Val
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Ser Ala  Leu Leu Leu Ala Ala  Gly Cys Trp Gly Gln  Val Thr Leu
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Thr Val  Thr Val Thr Ala Ala  Thr Leu Leu Phe Cys  His Tyr Ala
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Tyr Met  Val Pro Gly Trp Gln  Ala Glu Ala Met Arg  Ser Ala Gln
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Arg Arg  Thr Ala Ala Gly Ile  Met Lys Asn Ala Val  Val Asp Gly
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Ile Val  Ala Thr Asp Val Pro  Glu Leu Glu Arg Thr  Thr Pro Ile
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Met Gln  Lys Lys Val Gly Gln  Ile Met Leu Ile Leu  Val Ser Leu
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Ile Met  Arg Gly Gly Trp Leu  Ser Cys Leu Ser Ile  Thr Trp Thr
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Leu Ile  Lys Asn Met Glu Lys  Pro Gly Leu Lys Arg  Gly Gly Ala
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Lys Gly  Arg Thr Leu Gly Glu  Val Trp Lys Glu Arg  Leu Asn Gln
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Met Thr  Lys Glu Glu Phe Thr  Arg Tyr Arg Lys Glu  Ala Ile Ile
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Asp Leu  Gly Cys Gly Arg Gly  Gly Trp Cys Tyr Tyr  Met Ala Thr
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Gln Lys  Arg Val Gln Glu Val  Arg Gly Tyr Thr Lys  Gly Gly Pro
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Gly His  Glu Glu Pro Gln Leu  Val Gln Ser Tyr Gly  Trp Asn Ile
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Val Thr  Met Lys Ser Gly Val  Asp Val Phe Tyr Arg  Pro Ser Glu
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Cys Cys  Asp Thr Leu Leu Cys  Asp Ile Gly Glu Ser  Ser Ser Ser
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Ala Glu  Val Glu Glu His Arg  Thr Ile Arg Val Leu  Glu Met Val
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Glu Asp  Trp Leu His Arg Gly  Pro Arg Glu Phe Cys  Val Lys Val
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Leu Cys  Pro Tyr Met Pro Lys  Val Ile Glu Lys Met  Glu Leu Leu
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Gln Arg  Arg Tyr Gly Gly Gly  Leu Val Arg Asn Pro  Leu Ser Arg
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Asn Ser  Thr His Glu Met Tyr  Trp Val Ser Arg Ala  Ser Gly Asn
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Val Val  His Ser Val Asn Met  Thr Ser Gln Val Leu  Leu Gly Arg
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Ser Asp  Thr Ser Lys Ile Lys  Asn Arg Ile Glu Arg  Leu Arg Arg
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Pro Asp  Asp Val Glu Lys Leu  Thr Lys Gly Lys Gly  Pro Lys Val
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Arg Thr  Trp Leu Phe Glu Asn  Gly Glu Glu Arg Leu  Ser Arg Met
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Ala Val  Ser Gly Asp Asp Cys  Val Val Lys Pro Leu  Asp Asp Arg
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Phe Ala  Thr Ser Leu His Phe  Leu Asn Ala Met Ser  Lys Val Arg
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Lys Asp  Ile Gln Glu Trp Lys  Pro Ser Thr Gly Trp  Tyr Asp Trp
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Gln Gln  Val Pro Phe Cys Ser  Asn His Phe Thr Glu  Leu Ile Met
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Lys Asp  Gly Arg Thr Leu Val  Val Pro Cys Arg Gly  Gln Asp Glu
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Arg Asp  Thr Ala Cys Leu Ala  Lys Ser Tyr Ala Gln  Met Trp Leu
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Leu Leu  Tyr Phe His Arg Arg  Asp Leu Arg Leu Met  Ala Asn Ala
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Ile Cys  Ser Ala Val Pro Val  Asn Trp Val Pro Thr  Gly Arg Thr
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Thr Trp  Ser Ile His Ala Gly  Gly Glu Trp Met Thr  Thr Glu Asp
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Met Leu  Glu Val Trp Asn Arg  Val Trp Ile Glu Glu  Asn Glu Trp
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Ser Gly  Lys Arg Glu Asp Ile  Trp Cys Gly Ser Leu  Ile Gly Thr
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Arg Ala  Arg Ala Thr Trp Ala  Glu Asn Ile Gln Val  Ala Ile Asn
    3680                 3685                 3690

Gln Val  Arg Ala Ile Ile Gly  Asp Glu Lys Tyr Val  Asp Tyr Met
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ccccggaaaa cgcaaaacag catattgacg ctgggaaaga ccagagactc catgagtttc  10740
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tgggtct                                                            10807
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<210> SEQ ID NO 14
<211> LENGTH: 3423
<212> TYPE: PRT
<213> ORGANISM: Zika virus strain R103451

<400> SEQUENCE: 14

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gly Ser Leu Val Thr Cys Ala Lys Phe Ala Cys Ser Lys Lys Met Thr
                405                 410                 415
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Gly Lys Ser Ile Gln Pro Glu Asn Leu Glu Tyr Arg Ile Met Leu Ser
            420                 425                 430

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Val Arg Gly Ala Lys Arg Met Ala Val Leu Gly Asp Thr Ala Trp Asp
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
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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 Ala 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
    1010                1015                1020

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

Lys Ser  Leu Ala Gly Pro Leu  Ser His His Asn Thr  Arg Glu Gly
    1040                1045                1050

Tyr Arg  Thr Gln Met Lys Gly  Pro Trp His Ser Glu  Glu Leu Glu
    1055                1060                1065

Ile Arg  Phe Glu Glu Cys Pro  Gly Thr Lys Val His  Val Glu Glu
    1070                1075                1080

Thr Cys  Gly Thr Arg Gly Pro  Ser Leu Arg Ser Thr  Thr Ala Ser
    1085                1090                1095

Gly Arg  Val Ile Glu Glu Trp  Cys Cys Arg Glu Cys  Thr Met Pro
    1100                1105                1110

Pro Leu  Ser Phe Arg Ala Lys  Asp Gly Cys Trp Tyr  Gly Met Glu
    1115                1120                1125

Ile Arg  Pro Arg Lys Glu Pro  Glu Ser Asn Leu Val  Arg Ser Met
    1130                1135                1140

Val Thr  Ala Gly Ser Thr Asp  His Met Asp His Phe  Ser Leu Gly
    1145                1150                1155

Val Leu  Val Ile Leu Leu Met  Val Gln Glu Gly Leu  Lys Lys Arg
    1160                1165                1170

Met Thr  Thr Lys Ile Ile Ile  Ser Thr Ser Met Ala  Val Leu Val
    1175                1180                1185

Ala Met  Ile Leu Gly Gly Phe  Ser Met Ser Asp Leu  Ala Lys Leu
    1190                1195                1200

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

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

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

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

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

Ala Leu Ala Trp Leu Ala Ile Arg Ala Met Val Val Pro Arg Thr
1280 1285 1290

Asp Asn Ile Thr Leu Ala Ile Leu Ala Ala Leu Thr Pro Leu Ala
1295 1300 1305

Arg Gly Thr Leu Leu Val Ala Trp Arg Ala Gly Leu Ala Thr Cys
1310 1315 1320

Gly Gly Phe Met Leu Leu Ser Leu Lys Gly Lys Gly Ser Val Lys
1325 1330 1335

Lys Asn Leu Pro Phe Val Met Ala Leu Gly Leu Thr Ala Val Arg
1340 1345 1350

Leu Val Asp Pro Ile Asn Val Val Gly Leu Leu Leu Leu Thr Arg
1355 1360 1365

Ser Gly Lys Arg Ser Trp Pro Pro Ser Glu Val Leu Thr Ala Val
1370 1375 1380

Gly Leu Ile Cys Ala Leu Ala Gly Gly Phe Ala Lys Ala Asp Ile
1385 1390 1395

Glu Met Ala Gly Pro Met Ala Ala Val Gly Leu Leu Ile Val Ser
1400 1405 1410

Tyr Val Val Ser Gly Lys Ser Val Asp Met Tyr Ile Glu Arg Ala
1415 1420 1425

Gly Asp Ile Thr Trp Glu Lys Asp Ala Glu Val Thr Gly Asn Ser
1430 1435 1440

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

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

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
1490 1495 1500

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

Glu Thr Thr Asp Gly Val Tyr Arg Val Met Thr Arg Arg Leu Leu
1520 1525 1530

Gly Ser Thr Gln Val Gly Val Gly Val Met Gln Glu Gly Val Phe
1535 1540 1545

His Thr Met Trp His Val Thr Lys Gly Ser Ala Leu Arg Ser Gly
1550 1555 1560

Glu Gly Arg Leu Asp Pro Tyr Trp Gly Asp Val Lys Gln Asp Leu
1565 1570 1575

Val Ser Tyr Cys Gly Pro Trp Lys Leu Asp Ala Ala Trp Asp Gly
1580 1585 1590

His Ser Glu Val Gln Leu Leu Ala Val Pro Pro Gly Glu Arg Ala
1595 1600 1605

Arg Asn Ile Gln Thr Leu Pro Gly Ile Phe Lys Thr Lys Asp Gly
1610 1615 1620

Asp Ile Gly Ala Val Ala Leu Asp Tyr Pro Ala Gly Thr Ser Gly
1625 1630 1635

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Ser Pro  Ile Leu Asp Lys Cys  Gly Arg Val Ile Gly  Leu Tyr Gly
    1640                 1645                 1650

Asn Gly  Val Val Ile Lys Asn  Gly Ser Tyr Val Ser  Ala Ile Thr
    1655                 1660                 1665

Gln Gly  Arg Arg Glu Glu Glu  Thr Pro Val Glu Cys  Phe Glu Pro
    1670                 1675                 1680

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

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

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
    1730                 1735                 1740

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

Ile Val  Asp Leu Met Cys His  Ala Thr Phe Thr Ser  Arg Leu Leu
    1760                 1765                 1770

Gln Pro  Ile Arg Val Pro Asn  Tyr Asn Leu Tyr Ile  Met Asp Glu
    1775                 1780                 1785

Ala His  Phe Thr Asp Pro Ser  Ser Ile Ala Ala Arg  Gly Tyr Ile
    1790                 1795                 1800

Ser Thr  Arg Val Glu Met Gly  Glu Ala Ala Ala Ile  Phe Met Thr
    1805                 1810                 1815

Ala Thr  Pro Pro Gly Thr Arg  Asp Ala Phe Pro Asp  Ser Asn Ser
    1820                 1825                 1830

Pro Ile  Met Asp Thr Glu Val  Glu Val Pro Glu Arg  Ala Trp Ser
    1835                 1840                 1845

Ser Gly  Phe Asp Trp Val Thr  Asp His Ser Gly Lys  Thr Val Trp
    1850                 1855                 1860

Phe Val  Pro Ser Val Arg Asn  Gly Asn Glu Ile Ala  Ala Cys Leu
    1865                 1870                 1875

Thr Lys  Ala Gly Lys Arg Val  Ile Gln Leu Ser Arg  Lys Thr Phe
    1880                 1885                 1890

Glu Thr  Glu Phe Gln Lys Thr  Lys His Gln Glu Trp  Asp Phe Val
    1895                 1900                 1905

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

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

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

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

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

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

Ile Tyr  Leu Gln Asp Gly Leu  Ile Ala Ser Leu Tyr  Arg Pro Glu
    2000                 2005                 2010

Ala Asp  Lys Val Ala Ala Ile  Glu Gly Glu Phe Lys  Leu Arg Thr
    2015                 2020                 2025
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Glu Gln  Arg Lys Thr Phe Val  Glu Leu Met Lys Arg  Gly Asp Leu
    2030                 2035                 2040

Pro Val  Trp Leu Ala Tyr Gln  Val Ala Ser Ala Gly  Ile Thr Tyr
    2045                 2050                 2055

Thr Asp  Arg Arg Trp Cys Phe  Asp Gly Thr Thr Asn  Asn Thr Ile
    2060                 2065                 2070

Leu Glu  Asp Ser Val Pro Ala  Glu Val Trp Thr Arg  His Gly Glu
    2075                 2080                 2085

Lys Arg  Val Leu Lys Pro Arg  Trp Met Asp Ala Arg  Val Cys Ser
    2090                 2095                 2100

Asp His  Ala Ala Leu Lys Ser  Phe Lys Glu Phe Ala  Ala Gly Lys
    2105                 2110                 2115

Arg Gly  Ala Ala Phe Gly Val  Met Glu Ala Leu Gly  Thr Leu Pro
    2120                 2125                 2130

Gly His  Met Thr Glu Arg Phe  Gln Glu Ala Ile Asp  Asn Leu Ala
    2135                 2140                 2145

Val Leu  Met Arg Ala Glu Thr  Gly Ser Arg Pro Tyr  Lys Ala Ala
    2150                 2155                 2160

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

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

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
    2210                 2215                 2220

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

Ile Pro  Glu Pro Glu Lys Gln  Arg Ser Pro Gln Asp  Asn Gln Met
    2240                 2245                 2250

Ala Ile  Ile Ile Met Val Ala  Val Gly Leu Leu Gly  Leu Ile Thr
    2255                 2260                 2265

Ala Asn  Glu Leu Gly Trp Leu  Glu Arg Thr Lys Ser  Asp Leu Ser
    2270                 2275                 2280

His Leu  Met Gly Arg Arg Glu  Glu Gly Ala Thr Ile  Gly Phe Ser
    2285                 2290                 2295

Met Asp  Ile Asp Leu Arg Pro  Ala Ser Ala Trp Ala  Ile Tyr Ala
    2300                 2305                 2310

Ala Leu  Thr Thr Phe Ile Thr  Pro Ala Val Gln His  Ala Val Thr
    2315                 2320                 2325

Thr Ser  Tyr Asn Asn Tyr Ser  Leu Met Ala Met Ala  Thr Gln Ala
    2330                 2335                 2340

Gly Val  Leu Phe Gly Met Gly  Lys Gly Met Pro Phe  Tyr Ala Trp
    2345                 2350                 2355

Asp Phe  Gly Val Pro Leu Leu  Met Ile Gly Cys Tyr  Ser Gln Leu
    2360                 2365                 2370

Thr Pro  Leu Thr Leu Ile Val  Ala Ile Ile Leu Leu  Val Ala His
    2375                 2380                 2385

Tyr Met  Tyr Leu Ile Pro Gly  Leu Gln Ala Ala Ala  Ala Arg Ala
    2390                 2395                 2400

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

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

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
    2450                2455                2460

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

Ser Pro  Asn Lys Tyr Trp Asn  Ser Ser Thr Ala Thr  Ser Leu Cys
    2480                2485                2490

Asn Ile  Phe Arg Gly Ser Tyr  Leu Ala Gly Ala Ser  Leu Ile Tyr
    2495                2500                2505

Thr Val  Thr Arg Asn Ala Gly  Leu Val Lys Arg Arg  Gly Gly Gly
    2510                2515                2520

Thr Gly  Glu Thr Leu Gly Glu  Lys Trp Lys Ala Arg  Leu Asn Gln
    2525                2530                2535

Met Ser  Ala Leu Glu Phe Tyr  Ser Tyr Lys Lys Ser  Gly Ile Thr
    2540                2545                2550

Glu Val  Cys Arg Glu Glu Ala  Arg Arg Ala Leu Lys  Asp Gly Val
    2555                2560                2565

Ala Thr  Gly Gly His Ala Val  Ser Arg Gly Ser Ala  Lys Leu Arg
    2570                2575                2580

Trp Leu  Val Glu Arg Gly Tyr  Leu Gln Pro Tyr Gly  Lys Val Ile
    2585                2590                2595

Asp Leu  Gly Cys Gly Arg Gly  Gly Trp Ser Tyr Tyr  Ala Ala Thr
    2600                2605                2610

Ile Arg  Lys Val Gln Glu Val  Lys Gly Tyr Thr Lys  Gly Gly Pro
    2615                2620                2625

Gly His  Glu Glu Pro Val Leu  Val Gln Ser Tyr Gly  Trp Asn Ile
    2630                2635                2640

Val Arg  Leu Lys Ser Gly Val  Asp Val Phe His Met  Ala Ala Glu
    2645                2650                2655

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

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
    2690                2695                2700

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

Gln Arg  Arg Tyr Gly Gly Gly  Leu Val Arg Val Pro  Leu Ser Arg
    2720                2725                2730

Asn Ser  Thr His Glu Met Tyr  Trp Val Ser Gly Ala  Lys Ser Asn
    2735                2740                2745

Thr Ile  Lys Ser Val Ser Thr  Thr Ser Gln Leu Leu  Leu Gly Arg
    2750                2755                2760

Met Asp  Gly Pro Arg Arg Pro  Val Lys Tyr Glu Glu  Asp Val Asn
    2765                2770                2775

Leu Gly  Ser Gly Thr Arg Ala  Val Val Ser Cys Ala  Glu Ala Pro
    2780                2785                2790

Asn Met  Lys Ile Ile Gly Asn  Arg Ile Glu Arg Ile  Arg Ser Glu
    2795                2800                2805

His Ala  Glu Thr Trp Phe Phe  Asp Glu Asn His Pro  Tyr Arg Thr
    2810                2815                2820
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Trp Ala  Tyr His Gly Ser Tyr  Glu Ala Pro Thr Gln  Gly Ser Ala
    2825                 2830                 2835

Ser Ser  Leu Ile Asn Gly Val  Val Arg Leu Leu Ser  Lys Pro Trp
    2840                 2845                 2850

Asp Val  Val Thr Gly Val Thr  Gly Ile Ala Met Thr  Asp Thr Thr
    2855                 2860                 2865

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

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

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

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
    2930                 2935                 2940

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

Glu Arg  Glu His His Leu Arg  Gly Glu Cys Gln Ser  Cys Val Tyr
    2960                 2965                 2970

Asn Met  Met Gly Lys Arg Glu  Lys Lys Gln Gly Glu  Phe Gly Lys
    2975                 2980                 2985

Ala Lys  Gly Ser Arg Ala Ile  Trp Tyr Met Trp Leu  Gly Ala Arg
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Phe Leu  Glu Phe Glu Ala Leu  Gly Phe Leu Asn Glu  Asp His Trp
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Gln Arg  Leu Gly Tyr Val Leu  Glu Glu Met Ser Cys  Ile Pro Gly
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Ser Arg  Phe Asp Leu Glu Asn  Glu Ala Leu Ile Thr  Asn Gln Met
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Glu Lys  Gly His Arg Ala Leu  Ala Leu Ala Ile Ile  Lys Tyr Thr
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Tyr Gln  Asn Lys Val Val Lys  Val Leu Arg Pro Ala  Glu Lys Gly
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Lys Thr  Val Met Asp Ile Ile  Ser Arg Gln Asp Gln  Arg Gly Ser
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Gly Asp  Asp Cys Val Val Lys  Pro Ile Asp Asp Arg  Phe Ala His
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Arg Ala  Arg Val Ser Pro Gly  Ala Gly Trp Ser Ile  Arg Glu Thr
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Ala Cys  Leu Ala Lys Ser Tyr  Ala Gln Met Trp Gln  Leu Leu Tyr
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Phe His  Arg Arg Asp Leu Arg  Leu Met Ala Asn Ala  Ile Cys Ser
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Ser Val  Pro Val Asp Trp Val  Pro Thr Gly Arg Thr  Thr Trp Ser
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Ile His  Gly Lys Gly Glu Trp  Met Thr Thr Glu Asp  Met Leu Val
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Val Trp  Asn Arg Val Trp Ile  Glu Glu Asn Asp His  Met Glu Asp
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Arg Ile  Ile Gly Asp Glu Glu  Lys Tyr Met Asp Tyr  Leu Ser Thr
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Ile Lys Lys Phe Lys Lys Asp Leu Ala Ala Met Leu Arg Ile Ile Asn
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Val Gly Leu Leu Leu Thr Thr Ala Met Ala Ala Glu Val Thr Arg Arg
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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
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Tyr Ser Ile Arg Cys Ile Gly Val Ser Asn Arg Asp Phe Val Glu Gly
    290                 295                 300

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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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-continued

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705                 710                 715                 720

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

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

Phe Ser Gln Ile Leu Ile Gly Thr Leu Leu 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
    1010                1015                1020

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

Lys Ser  Leu Ala Gly Pro Leu  Ser His His Asn Thr  Arg Glu Gly
    1040                1045                1050

Tyr Arg  Thr Gln Met Lys Gly  Pro Trp His Ser Glu  Glu Leu Glu
    1055                1060                1065

Ile Arg  Phe Glu Glu Cys Pro  Gly Thr Lys Val His  Val Glu Glu
    1070                1075                1080

Thr Cys  Gly Thr Arg Gly Pro  Ser Leu Arg Ser Thr  Thr Ala Ser
    1085                1090                1095

Gly Arg  Val Ile Glu Glu Trp  Cys Cys Arg Glu Cys  Thr Met Pro
    1100                1105                1110

Pro Leu  Ser Phe Arg Ala Lys  Asp Gly Cys Trp Tyr  Gly Met Glu
    1115                1120                1125
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Ile Arg  Pro Arg Lys Glu Pro  Glu Ser Asn Leu Val  Arg Ser Met
    1130                 1135                 1140

Val Thr  Ala Gly Ser Thr Asp  His Met Asp His Phe  Ser Leu Gly
    1145                 1150                 1155

Val Leu  Val Ile Leu Leu Met  Val Gln Glu Gly Leu  Lys Lys Arg
    1160                 1165                 1170

Met Thr  Thr Lys Ile Ile Ile  Ser Thr Ser Met Ala  Val Leu Val
    1175                 1180                 1185

Ala Met  Ile Leu Gly Gly Phe  Ser Met Ser Asp Leu  Ala Lys Leu
    1190                 1195                 1200

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

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

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
    1250                 1255                 1260

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

Ala Leu  Ala Trp Leu Ala Ile  Arg Ala Met Val Val  Pro Arg Thr
    1280                 1285                 1290

Asp Asn  Ile Thr Leu Ala Ile  Leu Ala Ala Leu Thr  Pro Leu Ala
    1295                 1300                 1305

Arg Gly  Thr Leu Leu Val Ala  Trp Arg Ala Gly Leu  Ala Thr Cys
    1310                 1315                 1320

Gly Gly  Phe Met Leu Leu Ser  Leu Lys Gly Lys Gly  Ser Val Lys
    1325                 1330                 1335

Lys Asn  Leu Pro Phe Val Met  Ala Leu Gly Leu Thr  Ala Val Arg
    1340                 1345                 1350

Leu Val  Asp Pro Ile Asn Val  Val Gly Leu Leu Leu  Leu Thr Arg
    1355                 1360                 1365

Ser Gly  Lys Arg Ser Trp Pro  Pro Ser Glu Val Leu  Thr Ala Val
    1370                 1375                 1380

Gly Leu  Ile Cys Ala Leu Ala  Gly Gly Phe Ala Lys  Ala Asp Ile
    1385                 1390                 1395

Glu Met  Ala Gly Pro Met Ala  Ala Val Gly Leu Leu  Ile Val Ser
    1400                 1405                 1410

Tyr Val  Val Ser Gly Lys Ser  Val Asp Met Tyr Ile  Glu Arg Ala
    1415                 1420                 1425

Gly Asp  Ile Thr Trp Glu Lys  Asp Ala Glu Val Thr  Gly Asn Ser
    1430                 1435                 1440

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

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

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
    1490                 1495                 1500

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

Gly Ser Thr Gln Val Gly Val Gly Val Met Gln Glu Gly Val Phe
1535 1540 1545

His Thr Met Trp His Val Thr Lys Gly Ser Ala Leu Arg Ser Gly
1550 1555 1560

Glu Gly Arg Leu Asp Pro Tyr Trp Gly Asp Val Lys Gln Asp Leu
1565 1570 1575

Val Ser Tyr Cys Gly Pro Trp Lys Leu Asp Ala Ala Trp Asp Gly
1580 1585 1590

His Ser Glu Val Gln Leu Leu Ala Val Pro Pro Gly Glu Arg Ala
1595 1600 1605

Arg Asn Ile Gln Thr Leu Pro Gly Ile Phe Lys Thr Lys Asp Gly
1610 1615 1620

Asp Ile Gly Ala Val Ala Leu Asp Tyr Pro Ala Gly Thr Ser Gly
1625 1630 1635

Ser Pro Ile Leu Asp Lys Cys Gly Arg Val Ile Gly Leu Tyr Gly
1640 1645 1650

Asn Gly Val Val Ile Lys Asn Gly Ser Tyr Val Ser Ala Ile Thr
1655 1660 1665

Gln Gly Arg Arg Glu Glu Glu Thr Pro Val Glu Cys Phe Glu Pro
1670 1675 1680

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

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

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
1730 1735 1740

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

Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Ser Arg Leu Leu
1760 1765 1770

Gln Pro Ile Arg Val Pro Asn Tyr Asn Leu Tyr Ile Met Asp Glu
1775 1780 1785

Ala His Phe Thr Asp Pro Ser Ser Ile Ala Ala Arg Gly Tyr Ile
1790 1795 1800

Ser Thr Arg Val Glu Met Gly Glu Ala Ala Ala Ile Phe Met Thr
1805 1810 1815

Ala Thr Pro Pro Gly Thr Arg Asp Ala Phe Pro Asp Ser Asn Ser
1820 1825 1830

Pro Ile Met Asp Thr Glu Val Glu Val Pro Glu Arg Ala Trp Ser
1835 1840 1845

Ser Gly Phe Asp Trp Val Thr Asp His Ser Gly Lys Thr Val Trp
1850 1855 1860

Phe Val Pro Ser Val Arg Asn Gly Asn Glu Ile Ala Ala Cys Leu
1865 1870 1875

Thr Lys Ala Gly Lys Arg Val Ile Gln Leu Ser Arg Lys Thr Phe
1880 1885 1890

Glu Thr Glu Phe Gln Lys Thr Lys His Gln Glu Trp Asp Phe Val
1895 1900 1905

Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys Ala Asp

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    1910                1915                1920

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

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

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

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

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

Ile Tyr  Leu Gln Asp Gly Leu  Ile Ala Ser Leu Tyr  Arg Pro Glu
    2000                2005                2010

Ala Asp  Lys Val Ala Ala Ile  Glu Gly Glu Phe Lys  Leu Arg Thr
    2015                2020                2025

Glu Gln  Arg Lys Thr Phe Val  Glu Leu Met Lys Arg  Gly Asp Leu
    2030                2035                2040

Pro Val  Trp Leu Ala Tyr Gln  Val Ala Ser Ala Gly  Ile Thr Tyr
    2045                2050                2055

Thr Asp  Arg Arg Trp Cys Phe  Asp Gly Thr Thr Asn  Asn Thr Ile
    2060                2065                2070

Met Glu  Asp Ser Val Pro Ala  Glu Val Trp Thr Arg  His Gly Glu
    2075                2080                2085

Lys Arg  Val Leu Lys Pro Arg  Trp Met Asp Ala Arg  Val Cys Ser
    2090                2095                2100

Asp His  Ala Ala Leu Lys Ser  Phe Lys Glu Phe Ala  Ala Gly Lys
    2105                2110                2115

Arg Gly  Ala Ala Phe Gly Val  Met Glu Ala Leu Gly  Thr Leu Pro
    2120                2125                2130

Gly His  Met Thr Glu Arg Phe  Gln Glu Ala Ile Asp  Asn Leu Ala
    2135                2140                2145

Val Leu  Met Arg Ala Glu Thr  Gly Ser Arg Pro Tyr  Lys Ala Ala
    2150                2155                2160

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

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

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
    2210                2215                2220

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

Ile Pro  Glu Pro Glu Lys Gln  Arg Ser Pro Gln Asp  Asn Gln Met
    2240                2245                2250

Ala Ile  Ile Ile Met Val Ala  Val Gly Leu Leu Gly  Leu Ile Thr
    2255                2260                2265

Ala Asn  Glu Leu Gly Trp Leu  Glu Arg Thr Lys Ser  Asp Leu Ser
    2270                2275                2280

His Leu  Met Gly Arg Arg Glu  Glu Gly Ala Thr Ile  Gly Phe Ser
    2285                2290                2295

Met Asp  Ile Asp Leu Arg Pro  Ala Ser Ala Trp Ala  Ile Tyr Ala
    2300                2305                2310
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Ala Leu  Thr Thr Phe Ile Thr  Pro Ala Val Gln His  Ala Val Thr
    2315                 2320                 2325

Thr Ser  Tyr Asn Asn Tyr Ser  Leu Met Ala Met Ala  Thr Gln Ala
    2330                 2335                 2340

Gly Val  Leu Phe Gly Met Gly  Lys Gly Met Pro Phe  Tyr Ala Trp
    2345                 2350                 2355

Asp Phe  Gly Val Pro Leu Leu  Met Ile Gly Cys Tyr  Ser Gln Leu
    2360                 2365                 2370

Thr Pro  Leu Thr Leu Ile Val  Ala Ile Ile Leu Leu  Val Ala His
    2375                 2380                 2385

Tyr Met  Tyr Leu Ile Pro Gly  Leu Gln Ala Ala Ala  Ala Arg Ala
    2390                 2395                 2400

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

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

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
    2450                 2455                 2460

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

Ser Pro  Asn Lys Tyr Trp Asn  Ser Ser Thr Ala Thr  Ser Leu Cys
    2480                 2485                 2490

Asn Ile  Phe Arg Gly Ser Tyr  Leu Ala Gly Ala Ser  Leu Ile Tyr
    2495                 2500                 2505

Thr Val  Thr Arg Asn Ala Gly  Leu Val Lys Arg Arg  Gly Gly Gly
    2510                 2515                 2520

Thr Gly  Glu Thr Leu Gly Glu  Lys Trp Lys Ala Arg  Leu Asn Gln
    2525                 2530                 2535

Met Ser  Ala Leu Glu Phe Tyr  Ser Tyr Lys Lys Ser  Gly Ile Thr
    2540                 2545                 2550

Glu Val  Cys Arg Glu Glu Ala  Arg Arg Ala Leu Lys  Asp Gly Val
    2555                 2560                 2565

Ala Thr  Gly Gly His Ala Val  Ser Arg Gly Ser Ala  Lys Leu Arg
    2570                 2575                 2580

Trp Leu  Val Glu Arg Gly Tyr  Leu Gln Pro Tyr Gly  Lys Val Ile
    2585                 2590                 2595

Asp Leu  Gly Cys Gly Arg Gly  Gly Trp Ser Tyr Tyr  Val Ala Thr
    2600                 2605                 2610

Ile Arg  Lys Val Gln Glu Val  Lys Gly Tyr Thr Lys  Gly Gly Pro
    2615                 2620                 2625

Gly His  Glu Glu Pro Val Leu  Val Gln Ser Tyr Gly  Trp Asn Ile
    2630                 2635                 2640

Val Arg  Leu Lys Ser Gly Val  Asp Val Phe His Met  Ala Ala Glu
    2645                 2650                 2655

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

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
    2690                 2695                 2700
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Leu Cys  Pro Tyr Thr Ser Thr  Met Met Glu Thr Leu  Glu Arg Leu
    2705                 2710                 2715

Gln Arg  Arg Tyr Gly Gly Gly  Leu Val Arg Val Pro  Leu Ser Arg
    2720                 2725                 2730

Asn Ser  Thr His Glu Met Tyr  Trp Val Ser Gly Ala  Lys Ser Asn
    2735                 2740                 2745

Thr Ile  Lys Ser Val Ser Thr  Thr Ser Gln Leu Leu  Leu Gly Arg
    2750                 2755                 2760

Met Asp  Gly Pro Arg Arg Pro  Val Lys Tyr Glu Glu  Asp Val Asn
    2765                 2770                 2775

Leu Gly  Ser Gly Thr Arg Ala  Val Val Ser Cys Ala  Glu Ala Pro
    2780                 2785                 2790

Asn Met  Lys Ile Ile Gly Asn  Arg Ile Glu Arg Ile  Arg Ser Glu
    2795                 2800                 2805

His Ala  Glu Thr Trp Phe Phe  Asp Glu Asn His Pro  Tyr Arg Thr
    2810                 2815                 2820

Trp Ala  Tyr His Gly Ser Tyr  Glu Ala Pro Thr Gln  Gly Ser Ala
    2825                 2830                 2835

Ser Ser  Leu Ile Asn Gly Val  Val Arg Leu Leu Ser  Lys Pro Trp
    2840                 2845                 2850

Asp Val  Val Thr Gly Val Thr  Gly Ile Ala Met Thr  Asp Thr Thr
    2855                 2860                 2865

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

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

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

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
    2930                 2935                 2940

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

Glu Arg  Glu His His Leu Arg  Gly Glu Cys Gln Ser  Cys Val Tyr
    2960                 2965                 2970

Asn Met  Met Gly Lys Arg Glu  Lys Lys Gln Gly Glu  Phe Gly Lys
    2975                 2980                 2985

Ala Lys  Gly Ser Arg Ala Ile  Trp Tyr Met Trp Leu  Gly Ala Arg
    2990                 2995                 3000

Phe Leu  Glu Phe Glu Ala Leu  Gly Phe Leu Asn Glu  Asp His Trp
    3005                 3010                 3015

Met Gly  Arg Glu Asn Ser Gly  Gly Gly Val Glu Gly  Leu Gly Leu
    3020                 3025                 3030

Gln Arg  Leu Gly Tyr Val Leu  Glu Glu Met Ser Arg  Ile Pro Gly
    3035                 3040                 3045

Gly Arg  Met Tyr Ala Asp Asp  Thr Ala Gly Trp Asp  Thr Arg Ile
    3050                 3055                 3060

Ser Arg  Phe Asp Leu Glu Asn  Glu Ala Leu Ile Thr  Asn Gln Met
    3065                 3070                 3075

Glu Lys  Gly His Arg Ala Leu  Ala Leu Ala Ile Ile  Lys Tyr Thr
    3080                 3085                 3090

Tyr Gln  Asn Lys Val Val Lys  Val Leu Arg Pro Ala  Glu Lys Gly
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    3095                3100                3105

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

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

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

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
    3170                3175                3180

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

Ala Leu  Arg Phe Leu Asn Asp  Met Gly Lys Val Arg  Lys Asp Thr
    3200                3205                3210

Gln Glu  Trp Lys Pro Ser Thr  Gly Trp Asp Asn Trp  Glu Glu Val
    3215                3220                3225

Pro Phe  Cys Ser His His Phe  Asn Lys Leu His Leu  Lys Asp Gly
    3230                3235                3240

Arg Ser  Ile Val Val Pro Cys  Arg His Gln Asp Glu  Leu Ile Gly
    3245                3250                3255

Arg Ala  Arg Val Ser Pro Gly  Ala Gly Trp Ser Ile  Arg Glu Thr
    3260                3265                3270

Ala Cys  Leu Ala Lys Ser Tyr  Ala Gln Met Trp Gln  Leu Leu Tyr
    3275                3280                3285

Phe His  Arg Arg Asp Leu Arg  Leu Met Ala Asn Ala  Ile Cys Ser
    3290                3295                3300

Ser Val  Pro Val Asp Trp Val  Pro Thr Gly Arg Thr  Thr Trp Ser
    3305                3310                3315

Ile His  Gly Lys Gly Glu Trp  Met Thr Thr Glu Asp  Met Leu Val
    3320                3325                3330

Val Trp  Asn Arg Val Trp Ile  Glu Glu Asn Asp His  Met Glu Asp
    3335                3340                3345

Lys Thr  Pro Val Thr Lys Trp  Thr Asp Ile Pro Tyr  Leu Gly Lys
    3350                3355                3360

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

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

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

Gln Val  Arg Tyr Leu Gly Glu  Glu Gly Ser Thr Pro  Gly Val Leu
    3410                3415                3420
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<210> SEQ ID NO 17
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<212> TYPE: DNA
<213> ORGANISM: West Nile virus

<400> SEQUENCE: 17

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<211> LENGTH: 3433
<212> TYPE: PRT
<213> ORGANISM: West Nile virus

<400> SEQUENCE: 18

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Ala Met Leu Ser Leu Ile Asp Gly Lys Gly Pro Ile Arg Phe Val Leu
        35                  40                  45

Ala Leu Leu Ala Phe Phe Arg Phe Thr Ala Ile Ala Pro Thr Arg Ala
    50                  55                  60

Val Leu Asp Arg Trp Arg Gly Val Asn Lys Gln Thr Ala Met Lys His
65                  70                  75                  80

Leu Leu Ser Phe Lys Lys Glu Leu Gly Thr Leu Thr Ser Ala Ile Asn
                85                  90                  95

Arg Arg Ser Ser Lys Gln Lys Lys Arg Gly Gly Lys Thr Gly Ile Ala
            100                 105                 110

Val Met Ile Gly Leu Ile Ala Ser Val Gly Ala Val Thr Leu Ser Asn
        115                 120                 125

Phe Gln Gly Lys Val Met Met Thr Val Asn Ala Thr Asp Val Thr Asp
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Val Ile Thr Ile Pro Thr Ala Ala Gly Lys Asn Leu Cys Ile Val Arg
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Ala Met Asp Val Gly Tyr Met Cys Asp Asp Thr Ile Thr Tyr Glu Cys
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Pro Val Leu Ser Ala Gly Asn Asp Pro Glu Asp Ile Asp Cys Trp Cys
            180                 185                 190

Thr Lys Ser Ala Val Tyr Val Arg Tyr Gly Arg Cys Thr Lys Thr Arg
        195                 200                 205

His Ser Arg Arg Ser Arg Arg Ser Leu Thr Val Gln Thr His Gly Glu
    210                 215                 220

Ser Thr Leu Ala Asn Lys Lys Gly Ala Trp Met Asp Ser Thr Lys Ala
225                 230                 235                 240

Thr Arg Tyr Leu Val Lys Thr Glu Ser Trp Ile Leu Arg Asn Pro Gly
                245                 250                 255

Tyr Ala Leu Val Ala Ala Val Ile Gly Trp Met Leu Gly Ser Asn Thr
            260                 265                 270

Met Gln Arg Val Val Phe Val Val Leu Leu Leu Leu Val Ala Pro Ala
        275                 280                 285

Tyr Ser Phe Asn Cys Leu Gly Met Ser Asn Arg Asp Phe Leu Glu Gly
    290                 295                 300

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

Val Thr Ile Met Ser Lys Asp Lys Pro Thr Ile Asp Val Lys Met Met
                325                 330                 335

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

Ala Thr Val Ser Asp Leu Ser Thr Lys Ala Ala Cys Pro Thr Met Gly
        355                 360                 365

Glu Ala His Asn Asp Lys Arg Ala Asp Pro Ala Phe Val Cys Arg Gln
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Gly Val Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly Lys
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Gly Ser Ile Asp Thr Cys Ala Lys Phe Ala Cys Ser Thr Lys Ala Ile
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Gly Arg Thr Ile Leu Lys Glu Asn Ile Lys Tyr Glu Val Ala Ile Phe
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Val His Gly Pro Thr Thr Val Glu Ser His Gly Asn Tyr Ser Thr Gln
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Val Gly Ala Thr Gln Ala Gly Arg Phe Ser Ile Thr Pro Ala Ala Pro
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Ser Tyr Thr Leu Lys Leu Gly Glu Tyr Gly Glu Val Thr Val Asp Cys
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Glu Pro Arg Ser Gly Ile Asp Thr Asn Ala Tyr Tyr Val Met Thr Val
                485                 490                 495

Gly Thr Lys Thr Phe Leu Val His Arg Glu Trp Phe Met Asp Leu Asn
            500                 505                 510

Leu Pro Trp Ser Ser Ala Gly Ser Thr Val Trp Arg Asn Arg Glu Thr
        515                 520                 525

Leu Met Glu Phe Glu Glu Pro His Ala Thr Lys Gln Ser Val Ile Ala
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Leu Gly Ser Gln Glu Gly Ala Leu His Gln Ala Leu Ala Gly Ala Ile
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Lys Cys Arg Val Lys Met Glu Lys Leu Gln Leu Lys Gly Thr Thr Tyr
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Gly Val Cys Ser Lys Ala Phe Lys Phe Leu Gly Thr Pro Ala Asp Thr
        595                 600                 605

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

Pro Cys Lys Val Pro Ile Ser Ser Val Ala Ser Leu Asn Asp Leu Thr
625                 630                 635                 640

Pro Val Gly Arg Leu Val Thr Val Asn Pro Phe Val Ser Val Ala Thr
                645                 650                 655

Ala Asn Ala Lys Val Leu Ile Glu Leu Glu Pro Pro Phe Gly Asp Ser
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Tyr Ile Val Val Gly Arg Gly Glu Gln Gln Ile Asn His His Trp His
        675                 680                 685

Lys Ser Gly Ser Ser Ile Gly Lys Ala Phe Thr Thr Thr Leu Lys Gly
    690                 695                 700

Ala Gln Arg Leu Ala Ala Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser
705                 710                 715                 720

Val Gly Gly Val Phe Thr Ser Val Gly Lys Ala Val His Gln Val Phe
                725                 730                 735

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

Arg Ser Ile Ala Leu Thr Phe Leu Ala Val Gly Gly Val Leu Leu Phe
    770                 775                 780

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

Arg Gln Glu Leu Arg Cys Gly Ser Gly Val Phe Ile His Asn Asp Val
                805                 810                 815

Glu Ala Trp Met Asp Arg Tyr Lys Tyr Tyr Pro Glu Thr Pro Gln Gly
            820                 825                 830

Leu Ala Lys Ile Ile Gln Lys Ala His Lys Glu Gly Val Cys Gly Leu
        835                 840                 845

Arg Ser Val Ser Arg Leu Glu His Gln Met Trp Glu Ala Val Lys Asp
    850                 855                 860

Glu Leu Asn Thr Leu Leu Lys Glu Asn Gly Val Asp Leu Ser Val Val
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Val Glu Lys Gln Glu Gly Met Tyr Lys Ser Ala Pro Lys Arg Leu Thr
                885                 890                 895

Ala Thr Thr Glu Lys Leu Glu Ile Gly Trp Lys Ala Trp Gly Lys Ser
            900                 905                 910

Ile Leu Phe Ala Pro Glu Leu Ala Asn Asn Thr Phe Val Val Asp Gly
        915                 920                 925

Pro Glu Thr Lys Glu Cys Pro Thr Gln Asn Arg Ala Trp Asn Ser Leu
    930                 935                 940

Glu Val Glu Asp Phe Gly Phe Gly Leu Thr Ser Thr Arg Met Phe Leu
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Lys Val Arg Glu Ser Asn Thr Thr Glu Cys Asp Ser Lys Ile Ile Gly
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Gly Glu  Val Lys Ser Cys Thr  Trp Pro Glu Thr His  Thr Leu Trp
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Gly Asp  Gly Ile Leu Glu Ser  Asp Leu Ile Ile Pro  Val Thr Leu
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Ala Gly  Pro Arg Ser Asn His  Asn Arg Arg Pro Gly  Tyr Lys Thr
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Gln Asn  Gln Gly Pro Trp Asp  Glu Gly Arg Val Glu  Ile Asp Phe
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Asp Tyr  Cys Pro Gly Thr Thr  Val Thr Leu Ser Glu  Ser Cys Gly
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His Arg  Gly Pro Ala Thr Arg  Thr Thr Thr Glu Ser  Gly Lys Leu
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Ile Thr  Asp Trp Cys Cys Arg  Ser Cys Thr Leu Pro  Pro Leu Arg
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Tyr Gln  Thr Asp Ser Gly Cys  Trp Tyr Gly Met Glu  Ile Arg Pro
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Gln Arg  His Asp Glu Lys Thr  Leu Val Gln Ser Gln  Val Asn Ala
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Tyr Asn  Ala Asp Met Ile Asp  Pro Phe Gln Leu Gly  Leu Leu Val
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Val Phe  Leu Ala Thr Gln Glu  Val Leu Arg Lys Arg  Trp Thr Ala
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Lys Ile  Ser Met Pro Ala Ile  Leu Ile Ala Leu Leu  Val Leu Val
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Phe Gly  Gly Ile Thr Tyr Thr  Asp Val Leu Arg Tyr  Val Ile Leu
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Val Gly  Ala Ala Phe Ala Glu  Ser Asn Ser Gly Gly  Asp Val Val
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His Leu  Ala Leu Met Ala Thr  Phe Lys Ile Gln Pro  Val Phe Met
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Val Ala  Ser Phe Leu Lys Ala  Arg Trp Thr Asn Gln  Glu Asn Ile
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Leu Leu  Met Leu Ala Ala Val  Phe Phe Gln Met Ala  Tyr His Asp
    1250                 1255                 1260

Ala Arg  Gln Ile Leu Leu Trp  Glu Ile Pro Asp Val  Leu Asn Ser
    1265                 1270                 1275

Leu Ala  Val Ala Trp Met Ile  Leu Arg Ala Ile Thr  Phe Thr Thr
    1280                 1285                 1290

Thr Ser  Asn Val Val Val Pro  Leu Leu Ala Leu Leu  Thr Pro Gly
    1295                 1300                 1305

Leu Arg  Cys Leu Asn Leu Asp  Val Tyr Arg Ile Leu  Leu Leu Met
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Val Gly  Ile Gly Ser Leu Ile  Arg Glu Lys Arg Ser  Ala Ala Ala
    1325                 1330                 1335

Lys Lys  Lys Gly Ala Ser Leu  Leu Cys Leu Ala Leu  Ala Ser Thr
    1340                 1345                 1350

Gly Leu  Phe Asn Pro Met Ile  Leu Ala Ala Gly Leu  Ile Ala Cys
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Asp Pro  Asn Arg Lys Arg Gly  Trp Pro Ala Thr Glu  Val Met Thr
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Ala Val  Gly Leu Met Phe Ala  Ile Val Gly Gly Leu  Ala Glu Leu
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Asp Ile  Asp Ser Met Ala Ile  Pro Met Thr Ile Ala  Gly Leu Met
    1400                1405                1410

Phe Ala  Ala Phe Val Ile Ser  Gly Lys Ser Thr Asp  Met Trp Ile
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Glu Arg  Thr Ala Asp Ile Ser  Trp Glu Ser Asp Ala  Glu Ile Thr
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Gly Ser  Ser Glu Arg Val Asp  Val Arg Leu Asp Asp  Asp Gly Asn
    1445                1450                1455

Phe Gln  Leu Met Asn Asp Pro  Gly Ala Pro Trp Lys  Ile Trp Met
    1460                1465                1470

Leu Arg  Met Val Cys Leu Ala  Ile Ser Ala Tyr Thr  Pro Trp Ala
    1475                1480                1485

Ile Leu  Pro Ser Val Val Gly  Phe Trp Ile Thr Leu  Gln Tyr Thr
    1490                1495                1500

Lys Arg  Gly Gly Val Leu Trp  Asp Thr Pro Ser Pro  Lys Glu Tyr
    1505                1510                1515

Lys Lys  Gly Asp Thr Thr Thr  Gly Val Tyr Arg Ile  Met Thr Arg
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Gly Leu  Leu Gly Ser Tyr Gln  Ala Gly Ala Gly Val  Met Val Glu
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Gly Val  Phe His Thr Leu Trp  His Thr Thr Lys Gly  Ala Ala Leu
    1550                1555                1560

Met Ser  Gly Glu Gly Arg Leu  Asp Pro Tyr Trp Gly  Ser Val Lys
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Glu Asp  Arg Leu Cys Tyr Gly  Gly Pro Trp Lys Leu  Gln His Lys
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Trp Asn  Gly Gln Asp Glu Val  Gln Met Ile Val Val  Glu Pro Gly
    1595                1600                1605

Lys Asn  Val Lys Asn Val Gln  Thr Lys Pro Gly Val  Phe Lys Thr
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Pro Glu  Gly Glu Ile Gly Ala  Val Thr Leu Asp Phe  Pro Thr Gly
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Thr Ser  Gly Ser Pro Ile Val  Asp Lys Asn Gly Asp  Val Ile Gly
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Leu Tyr  Gly Asn Gly Val Ile  Met Pro Asn Gly Ser  Tyr Ile Ser
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Ala Ile  Val Gln Gly Glu Arg  Met Asp Glu Pro Ile  Pro Ala Gly
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Phe Glu  Pro Glu Met Leu Arg  Lys Lys Gln Ile Thr  Val Leu Asp
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Leu His  Pro Gly Ala Gly Lys  Thr Arg Arg Ile Leu  Pro Gln Ile
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Ile Lys  Glu Ala Ile Asn Arg  Arg Leu Arg Thr Ala  Val Leu Ala
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Pro Thr  Arg Val Val Ala Ala  Glu Met Ala Glu Ala  Leu Arg Gly
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Leu Pro  Ile Arg Tyr Gln Thr  Ser Ala Val Pro Arg  Glu His Asn
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Gly Asn  Glu Ile Val Asp Val  Met Cys His Ala Thr  Leu Thr His
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Met Asp  Glu Ala His Phe Thr  Asp Pro Ala Ser Ile  Ala Ala Arg
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Gly Tyr  Ile Ser Thr Lys Val  Glu Leu Gly Glu Ala  Ala Ala Ile
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Phe Met  Thr Ala Thr Pro Pro  Gly Thr Ser Asp Pro  Phe Pro Glu
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Ser Asn  Ser Pro Ile Ser Asp  Leu Gln Thr Glu Ile  Pro Asp Arg
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Ala Trp  Asn Ser Gly Tyr Glu  Trp Ile Thr Glu Tyr  Thr Gly Lys
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Thr Val  Trp Phe Val Pro Ser  Val Lys Met Gly Asn  Glu Ile Ala
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Leu Cys  Leu Gln Arg Ala Gly  Lys Lys Val Val Gln  Leu Asn Arg
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Lys Ser  Tyr Glu Thr Glu Tyr  Pro Lys Cys Lys Asn  Asp Asp Trp
    1895                 1900                 1905

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

Lys Ala  Ser Arg Val Ile Asp  Ser Arg Lys Ser Val  Lys Pro Thr
    1925                 1930                 1935

Ile Ile  Thr Glu Gly Glu Gly  Arg Val Ile Leu Gly  Glu Pro Ser
    1940                 1945                 1950

Ala Val  Thr Ala Ala Ser Ala  Ala Gln Arg Arg Gly  Arg Ile Gly
    1955                 1960                 1965

Arg Asn  Pro Ser Gln Val Gly  Asp Glu Tyr Cys Tyr  Gly Gly His
    1970                 1975                 1980

Thr Asn  Glu Asp Asp Ser Asn  Phe Ala His Trp Thr  Glu Ala Arg
    1985                 1990                 1995

Ile Met  Leu Asp Asn Ile Asn  Met Pro Asn Gly Leu  Ile Ala Gln
    2000                 2005                 2010

Phe Tyr  Gln Pro Glu Arg Glu  Lys Val Tyr Thr Met  Asp Gly Glu
    2015                 2020                 2025

Tyr Arg  Leu Arg Gly Glu Glu  Arg Lys Asn Phe Leu  Glu Leu Leu
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Arg Thr  Ala Asp Leu Pro Val  Trp Leu Ala Tyr Lys  Val Ala Ala
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Ala Gly  Val Ser Tyr His Asp  Arg Arg Trp Cys Phe  Asp Gly Pro
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Arg Thr  Asn Thr Ile Leu Glu  Asp Asn Asn Glu Val  Glu Val Ile
    2075                 2080                 2085

Thr Lys  Leu Gly Glu Arg Lys  Ile Leu Arg Pro Arg  Trp Ile Asp
    2090                 2095                 2100

Ala Arg  Val Tyr Ser Asp His  Gln Ala Leu Lys Ala  Phe Lys Asp
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Phe Ala  Ser Gly Lys Arg Ser  Gln Ile Gly Leu Ile  Glu Val Leu
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Gly Lys  Met Pro Glu His Phe  Met Gly Lys Thr Trp  Glu Ala Leu
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Asp Thr  Met Tyr Val Val Ala  Thr Ala Glu Lys Gly  Gly Arg Ala
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His Arg  Met Ala Leu Glu Glu  Leu Pro Asp Ala Leu  Gln Thr Ile
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Ala Leu  Ile Ala Leu Leu Ser  Val Met Thr Met Gly  Val Phe Phe
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Leu Leu  Met Gln Arg Lys Gly  Ile Gly Lys Ile Gly  Leu Gly Gly
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Ala Val  Leu Gly Val Ala Thr  Phe Phe Cys Trp Met  Ala Glu Val
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Pro Gly  Thr Lys Ile Ala Gly  Met Leu Leu Leu Ser  Leu Leu Leu
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Met Ile  Val Leu Ile Pro Glu  Pro Glu Lys Gln Arg  Ser Gln Thr
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Asp Asn  Gln Leu Ala Val Phe  Leu Ile Cys Val Met  Thr Leu Val
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Ser Ala  Val Ala Ala Asn Glu  Met Gly Trp Leu Asp  Lys Thr Lys
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Ser Asp  Ile Ser Ser Leu Phe  Gly Gln Arg Ile Glu  Val Lys Glu
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Asn Phe  Ser Met Gly Glu Phe  Leu Leu Asp Leu Arg  Pro Ala Thr
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Ala Trp  Ser Leu Tyr Ala Val  Thr Thr Ala Val Leu  Thr Pro Leu
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Leu Lys  His Leu Ile Thr Ser  Asp Tyr Ile Asn Thr  Ser Leu Thr
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Ser Ile  Asn Val Gln Ala Ser  Ala Leu Phe Thr Leu  Ala Arg Gly
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Phe Pro  Phe Val Asp Val Gly  Val Ser Ala Leu Leu  Leu Ala Ala
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Gly Cys  Trp Gly Gln Val Thr  Leu Thr Val Thr Val  Thr Ala Ala
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Thr Leu  Leu Phe Cys His Tyr  Ala Tyr Met Val Pro  Gly Trp Gln
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Met Lys  Asn Ala Val Val Asp  Gly Ile Val Ala Thr  Asp Val Pro
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Ser Val  Lys Thr Val Arg Glu  Ala Gly Ile Leu Ile  Thr Ala Ala
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Ala Val  Thr Leu Trp Glu Asn  Gly Ala Ser Ser Val  Trp Asn Ala
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Thr Thr  Ala Ile Gly Leu Cys  His Ile Met Arg Gly  Gly Trp Leu
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Ser Cys  Leu Ser Ile Thr Trp  Thr Leu Ile Lys Asn  Met Glu Lys
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Pro Gly  Leu Lys Arg Gly Gly  Ala Lys Gly Arg Thr  Leu Gly Glu
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Val Trp  Lys Glu Arg Leu Asn  Gln Met Thr Lys Glu  Glu Phe Thr
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Arg Tyr  Arg Lys Glu Ala Ile  Ile Glu Val Asp Arg  Ser Ala Ala
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Ser Arg  Gly Thr Ala Lys Leu  Arg Trp Leu Val Glu  Arg Arg Phe
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Leu Glu  Pro Val Gly Lys Val  Ile Asp Leu Gly Cys  Gly Arg Gly
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Gly Trp  Cys Tyr Tyr Met Ala  Thr Gln Lys Arg Val  Gln Glu Val
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Arg Gly  Tyr Thr Lys Gly Gly  Pro Gly His Glu Glu  Pro Gln Leu
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Val Gln  Ser Tyr Gly Trp Asn  Ile Val Thr Met Lys  Ser Gly Val
    2645                2650                2655

Asp Val  Phe Tyr Arg Pro Ser  Glu Cys Cys Asp Thr  Leu Leu Cys
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Asp Ile  Gly Glu Ser Ser Ser  Ser Ala Glu Val Glu  Glu His Arg
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Thr Ile  Arg Val Leu Glu Met  Val Glu Asp Trp Leu  His Arg Gly
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Pro Arg  Glu Phe Cys Val Lys  Val Leu Cys Pro Tyr  Met Pro Lys
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Val Ile  Glu Lys Met Glu Leu  Leu Gln Arg Arg Tyr  Gly Gly Gly
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Leu Val  Arg Asn Pro Leu Ser  Arg Asn Ser Thr His  Glu Met Tyr
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Trp Val  Ser Arg Ala Ser Gly  Asn Val Val His Ser  Val Asn Met
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Thr Ser  Gln Val Leu Leu Gly  Arg Met Glu Lys Arg  Thr Trp Lys
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Gly Pro  Gln Tyr Glu Glu Asp  Val Asn Leu Gly Ser  Gly Thr Arg
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Ala Val  Gly Lys Pro Leu Leu  Asn Ser Asp Thr Ser  Lys Ile Lys
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Asn Arg  Ile Glu Arg Leu Arg  Arg Glu Tyr Ser Ser  Thr Trp His
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His Asp  Glu Asn His Pro Tyr  Arg Thr Trp Asn Tyr  His Gly Ser
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Tyr Asp  Val Lys Pro Thr Gly  Ser Ala Ser Ser Leu  Val Asn Gly
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Val Val  Arg Leu Leu Ser Lys  Pro Trp Asp Thr Ile  Thr Asn Val
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Thr Thr  Met Ala Met Thr Asp  Thr Thr Pro Phe Gly  Gln Gln Arg
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Val Phe  Lys Glu Lys Val Asp  Thr Lys Ala Pro Glu  Pro Pro Glu
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Gly Val  Lys Tyr Val Leu Asn  Glu Thr Thr Asn Trp  Leu Trp Ala
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Phe Leu  Ala Arg Glu Lys Arg  Pro Arg Met Cys Ser  Arg Glu Glu
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Phe Ile  Arg Lys Val Asn Ser  Asn Ala Ala Leu Gly  Ala Met Phe
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Glu Glu  Gln Asn Gln Trp Arg  Ser Ala Arg Glu Ala  Val Glu Asp
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Arg Gly Glu Cys His Thr Cys Ile Tyr Asn Met Met Gly Lys Arg
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Glu Lys Lys Pro Gly Glu Phe Gly Lys Ala Lys Gly Ser Arg Ala
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Leu Gly Phe Leu Asn Glu Asp His Trp Leu Gly Arg Lys Asn Ser
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Gly Gly Gly Val Glu Gly Leu Gly Leu Gln Lys Leu Gly Tyr Ile
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Leu Arg Glu Val Gly Thr Arg Pro Gly Gly Lys Ile Tyr Ala Asp
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Asp Thr Ala Gly Trp Asp Thr Arg Ile Thr Arg Ala Asp Leu Glu
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Asn Glu Ala Lys Val Leu Glu Leu Leu Asp Gly Glu His Arg Arg
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Leu Ala Arg Ala Ile Ile Glu Leu Thr Tyr Arg His Lys Val Val
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Lys Val Met Arg Pro Ala Ala Asp Gly Arg Thr Val Met Asp Val
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Ile Ser Arg Glu Asp Gln Arg Gly Ser Gly Gln Val Val Thr Tyr
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Ala Leu Asn Thr Phe Thr Asn Leu Ala Val Gln Leu Val Arg Met
    3140                3145                3150

Met Glu Gly Glu Gly Val Ile Gly Pro Asp Asp Val Glu Lys Leu
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Thr Lys Gly Lys Gly Pro Lys Val Arg Thr Trp Leu Phe Glu Asn
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Gly Glu Glu Arg Leu Ser Arg Met Ala Val Ser Gly Asp Asp Cys
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Val Val Lys Pro Leu Asp Asp Arg Phe Ala Thr Ser Leu His Phe
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Leu Asn Ala Met Ser Lys Val Arg Lys Asp Ile Gln Glu Trp Lys
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Pro Ser Thr Gly Trp Tyr Asp Trp Gln Gln Val Pro Phe Cys Ser
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Asn His Phe Thr Glu Leu Ile Met Lys Asp Gly Arg Thr Leu Val
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Val Pro Cys Arg Gly Gln Asp Glu Leu Val Gly Arg Ala Arg Ile
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Ser Pro Gly Ala Gly Trp Asn Val Arg Asp Thr Ala Cys Leu Ala
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Lys Ser Tyr Ala Gln Met Trp Leu Leu Leu Tyr Phe His Arg Arg
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Asp Leu Arg Leu Met Ala Asn Ala Ile Cys Ser Ala Val Pro Val
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Asn Trp Val Pro Thr Gly Arg Thr Thr Trp Ser Ile His Ala Gly
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Gly Glu Trp Met Thr Thr Glu Asp Met Leu Glu Val Trp Asn Arg
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<223> OTHER INFORMATION: Synthetic polypeptide

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35 40 45

Met Lys Tyr Arg Met Glu Gly Cys Val Asp Gly His Lys Phe Val Ile
50 55 60

Thr Gly Glu Gly Ile Gly Tyr Pro Phe Lys Gly Lys Gln Ala Ile Asn
65 70 75 80

Leu Cys Val Val Glu Gly Gly Pro Leu Pro Phe Ala Glu Asp Ile Leu
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Ser Ala Ala Phe Met Tyr Gly Asn Arg Val Phe Thr Glu Tyr Pro Gln
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Asp Ile Ala Asp Tyr Phe Lys Asn Ser Cys Pro Ala Gly Tyr Thr Trp
115 120 125

Asp Arg Ser Phe Leu Phe Glu Asp Gly Ala Val Cys Ile Cys Asn Ala
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Asp Ile Thr Val Ser Val Glu Glu Asn Cys Met Tyr His Glu Ser Lys
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Phe Tyr Gly Val Asn Phe Pro Ala Asp Gly Pro Val Met Lys Lys Met
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Thr Asp Asn Trp Glu Pro Ser Cys Glu Lys Ile Ile Pro Val Pro Lys
180 185 190

Gln Gly Ile Leu Lys Gly Asp Val Ser Met Tyr Leu Leu Leu Lys Asp
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Gly Gly Arg Leu Arg Cys Gln Phe Asp Thr Val Tyr Lys Ala Lys Ser
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Val Pro Arg Lys Met Pro Asp Trp His Phe Ile Gln His Lys Leu Thr
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Arg Glu Asp Arg Ser Asp Ala Lys Asn Gln Lys Trp His Leu Thr Glu
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His Ala Ile Ala Ser Gly Ser Ala Leu Pro Gly Ser Gly Ala Thr Asn
            260                 265                 270

Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro
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Met Ser Lys Lys Pro Gly Gly Pro Gly Lys Ser Arg Ala Val Asn Met
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Leu Lys Arg Gly Met Pro Arg Val Leu Ser Leu Ile Gly Leu Lys Arg
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Ala Met Leu Ser Leu Ile Asp Gly Lys Gly Pro Ile Arg Phe Val Leu
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Ala Leu Leu Ala Phe Phe Arg Phe Thr Ala Ile Ala Pro Thr Arg Ala
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Val Leu Asp Arg Trp Arg Gly Val Asn Lys Gln Thr Ala Met Lys His
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Leu Leu Ser Phe Lys Lys Glu Leu Gly Thr Leu Thr Ser Ala Ile Asn
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Arg Arg Ser Ser Lys Gln Lys Lys Arg Gly Gly Lys Thr Gly Ile Ala
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Val Met Ile Gly Leu Ile Ala Ser Ala Met Ala Ala Glu Val Thr Arg
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Arg Gly Ser Ala Tyr Tyr Met Tyr Leu Asp Arg Asn Asp Ala Gly Glu
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Ala Ile Ser Phe Pro Thr Thr Leu Gly Met Asn Lys Cys Tyr Ile Gln
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Ile Met Asp Leu Gly His Met Cys Asp Ala Thr Met Ser Tyr Glu Cys
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Pro Met Leu Asp Glu Gly Val Glu Pro Asp Asp Val Asp Cys Trp Cys
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Asn Thr Thr Ser Thr Trp Val Val Tyr Gly Thr Cys His His Lys Lys
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Gly Glu Ala Arg Arg Ser Arg Arg Ala Val Thr Leu Pro Ser His Ser
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Thr Arg Lys Leu Gln Thr Arg Ser Gln Thr Trp Leu Glu Ser Arg Glu
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Tyr Thr Lys His Leu Ile Arg Val Glu Asn Trp Ile Phe Arg Asn Pro
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Gly Phe Ala Leu Ala Ala Ala Ala Ile Ala Trp Leu Leu Gly Ser Ser
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Thr Ser Gln Lys Val Ile Tyr Leu Val Met Ile Leu Leu Ile Ala Pro
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Ala Tyr Ser Ile Arg Cys Ile Gly Val Ser Asn Arg Asp Phe Val Glu
            580                 585                 590

Gly Met Ser Gly Gly Thr Trp Val Asp Val Val Leu Glu His Gly Gly
        595                 600                 605

Cys Val Thr Val Met Ala Gln Asp Lys Pro Thr Val Asp Ile Glu Leu
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Val Thr Thr Thr Val Ser Asn Met Ala Glu Val Arg Ser Tyr Cys Tyr
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Glu Ala Ser Ile Ser Asp Met Ala Ser Asp Ser Arg Cys Pro Thr Gln
                645                 650                 655

Gly Glu Ala Tyr Leu Asp Lys Gln Ser Asp Thr Gln Tyr Val Cys Lys
            660                 665                 670

Arg Thr Leu Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly
        675                 680                 685

Lys Gly Ser Leu Val Thr Cys Ala Lys Phe Ala Cys Ser Lys Lys Met
    690                 695                 700

Thr Gly Lys Ser Ile Gln Pro Glu Asn Leu Glu Tyr Arg Ile Met Leu
705                 710                 715                 720

Ser Val His Gly Ser Gln His Ser Gly Met Ile Val Asn Asp Thr Gly
                725                 730                 735

His Glu Thr Asp Glu Asn Arg Ala Lys Val Glu Ile Thr Pro Asn Ser
            740                 745                 750

Pro Arg Ala Glu Ala Thr Leu Gly Gly Phe Gly Ser Leu Gly Leu Asp
        755                 760                 765

Cys Glu Pro Arg Thr Gly Leu Asp Phe Ser Asp Leu Tyr Tyr Leu Thr
    770                 775                 780

Met Asn Asn Lys His Trp Leu Val His Lys Glu Trp Phe His Asp Ile
785                 790                 795                 800

Pro Leu Pro Trp His Ala Gly Ala Asp Thr Gly Thr Pro His Trp Asn
                805                 810                 815

Asn Lys Glu Ala Leu Val Glu Phe Lys Asp Ala His Ala Lys Arg Gln
            820                 825                 830

Thr Val Val Val Leu Gly Ser Gln Glu Gly Ala Val His Thr Ala Leu
        835                 840                 845

Ala Gly Ala Leu Glu Ala Glu Met Asp Gly Ala Lys Gly Arg Leu Ser
    850                 855                 860

Ser Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Arg Leu Lys
865                 870                 875                 880

Gly Val Ser Tyr Ser Leu Cys Thr Ala Ala Phe Thr Phe Thr Lys Ile
                885                 890                 895

Pro Ala Glu Thr Leu His Gly Thr Val Thr Val Glu Val Gln Tyr Ala
            900                 905                 910

Gly Thr Asp Gly Pro Cys Lys Val Pro Ala Gln Met Ala Val Asp Met
        915                 920                 925

Gln Thr Leu Thr Pro Val Gly Arg Leu Ile Thr Ala Asn Pro Val Ile
    930                 935                 940

Thr Glu Ser Thr Glu Asn Ser Lys Met Met Leu Glu Leu Asp Pro Pro
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Phe Gly Asp Ser Tyr Ile Val Ile Gly Val Gly Glu Lys Lys Ile Thr
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His His Trp His Arg Ser Gly Ser Thr Ile Gly Lys Ala Phe Glu Ala
            980                 985                 990

Thr Val Arg Gly Ala Lys Arg Met  Ala Val Leu Gly Asp  Thr Ala Trp
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Asp Phe  Gly Ser Val Gly Gly  Ala Leu Asn Ser Leu  Gly Lys Gly
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Ile His  Gln Ile Phe Gly Ala  Ala Phe Lys Ser Leu  Phe Gly Gly
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Met Ser  Trp Phe Ser Gln Ile  Leu Ile Gly Thr Leu  Leu Met Trp
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Leu Gly  Leu Asn Thr Lys Asn  Gly Ser Ile Ser Leu  Met Cys Leu
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Ala Leu  Gly Gly Val Leu Ile  Phe Leu Ser Thr Ala  Val Ser Ala
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Asp Ser  Gly Cys Ala Ile Asp  Ile Ser Arg Gln Glu  Leu Arg Cys
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Gly Ser  Gly Val Phe Ile His  Asn Asp Val Glu Ala  Trp Met Asp
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Arg Tyr  Lys Tyr Tyr Pro Glu  Thr Pro Gln Gly Leu  Ala Lys Ile
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Ile Gln  Lys Ala His Lys Glu  Gly Val Cys Gly Leu  Arg Ser Val
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Ser Arg  Leu Glu His Gln Met  Trp Glu Ala Val Lys  Asp Glu Leu
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Asn Thr  Leu Leu Lys Glu Asn  Gly Val Asp Leu Ser  Val Val Val
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Glu Lys  Gln Glu Gly Met Tyr  Lys Ser Ala Pro Lys  Arg Leu Thr
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Ala Thr  Thr Glu Lys Leu Glu  Ile Gly Trp Lys Ala  Trp Gly Lys
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Ser Ile  Leu Phe Ala Pro Glu  Leu Ala Asn Asn Thr  Phe Val Val
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Asp Gly  Pro Glu Thr Lys Glu  Cys Pro Thr Gln Asn  Arg Ala Trp
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Asn Ser  Leu Glu Val Glu Asp  Phe Gly Phe Gly Leu  Thr Ser Thr
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Arg Met  Phe Leu Lys Val Arg  Glu Ser Asn Thr Thr  Glu Cys Asp
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Ser Lys  Ile Ile Gly Thr Ala  Val Lys Asn Asn Leu  Ala Ile His
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Ser Asp  Leu Ser Tyr Trp Ile  Glu Ser Arg Leu Asn  Asp Thr Trp
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Lys Leu  Glu Arg Ala Val Leu  Gly Glu Val Lys Ser  Cys Thr Trp
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Pro Glu  Thr His Thr Leu Trp  Gly Asp Gly Ile Leu  Glu Ser Asp
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Leu Ile  Ile Pro Val Thr Leu  Ala Gly Pro Arg Ser  Asn His Asn
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Arg Arg  Pro Gly Tyr Lys Thr  Gln Asn Gln Gly Pro  Trp Asp Glu
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Gly Arg  Val Glu Ile Asp Phe  Asp Tyr Cys Pro Gly  Thr Thr Val
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Thr Leu  Ser Glu Ser Cys Gly  His Arg Gly Pro Ala  Thr Arg Thr
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Thr Thr  Glu Ser Gly Lys Leu  Ile Thr Asp Trp Cys  Cys Arg Ser
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Cys Thr  Leu Pro Pro Leu Arg  Tyr Gln Thr Asp Ser  Gly Cys Trp
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Tyr Gly  Met Glu Ile Arg Pro  Gln Arg His Asp Glu  Lys Thr Leu
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Val Gln  Ser Gln Val Asn Ala  Tyr Asn Ala Asp Met  Ile Asp Pro
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Phe Gln  Leu Gly Leu Leu Val  Val Phe Leu Ala Thr  Gln Glu Val
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Ile Ala  Leu Leu Val Leu Val  Phe Gly Gly Ile Thr  Tyr Thr Asp
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Val Leu  Arg Tyr Val Ile Leu  Val Gly Ala Ala Phe  Ala Glu Ser
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Asn Ser  Gly Gly Asp Val Val  His Leu Ala Leu Met  Ala Thr Phe
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Lys Ile  Gln Pro Val Phe Met  Val Ala Ser Phe Leu  Lys Ala Arg
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Trp Thr  Asn Gln Glu Asn Ile  Leu Leu Met Leu Ala  Ala Val Phe
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Ile Pro  Asp Val Leu Asn Ser  Leu Ala Val Ala Trp  Met Ile Leu
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Arg Ala  Ile Thr Phe Thr Thr  Thr Ser Asn Val Val  Val Pro Leu
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Leu Ala  Leu Leu Thr Pro Gly  Leu Arg Cys Leu Asn  Leu Asp Val
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Tyr Arg  Ile Leu Leu Leu Met  Val Gly Ile Gly Ser  Leu Ile Arg
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Glu Lys  Arg Ser Ala Ala Ala  Lys Lys Lys Gly Ala  Ser Leu Leu
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Cys Leu  Ala Leu Ala Ser Thr  Gly Leu Phe Asn Pro  Met Ile Leu
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Ala Ala  Gly Leu Ile Ala Cys  Asp Pro Asn Arg Lys  Arg Gly Trp
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Pro Ala  Thr Glu Val Met Thr  Ala Val Gly Leu Met  Phe Ala Ile
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Val Gly  Gly Leu Ala Glu Leu  Asp Ile Asp Ser Met  Ala Ile Pro
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Arg Leu  Asp Asp Asp Gly Asn  Phe Gln Leu Met Asn  Asp Pro Gly
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Ser Ala  Tyr Thr Pro Trp Ala  Ile Leu Pro Ser Val  Val Gly Phe
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Trp Ile  Thr Leu Gln Tyr Thr  Lys Arg Gly Gly Val  Leu Trp Asp
    1790                 1795                 1800

Thr Pro  Ser Pro Lys Glu Tyr  Lys Lys Gly Asp Thr  Thr Thr Gly
    1805                 1810                 1815

Val Tyr  Arg Ile Met Thr Arg  Gly Leu Leu Gly Ser  Tyr Gln Ala
    1820                 1825                 1830
```

```
Gly Ala  Gly Val Met Val Glu  Gly Val Phe His Thr  Leu Trp His
    1835                 1840                 1845

Thr Thr  Lys Gly Ala Ala Leu  Met Ser Gly Glu Gly  Arg Leu Asp
    1850                 1855                 1860

Pro Tyr  Trp Gly Ser Val Lys  Glu Asp Arg Leu Cys  Tyr Gly Gly
    1865                 1870                 1875

Pro Trp  Lys Leu Gln His Lys  Trp Asn Gly Gln Asp  Glu Val Gln
    1880                 1885                 1890

Met Ile  Val Val Glu Pro Gly  Arg Asn Val Lys Asn  Val Gln Thr
    1895                 1900                 1905

Lys Pro  Gly Val Phe Lys Thr  Pro Glu Gly Glu Ile  Gly Ala Val
    1910                 1915                 1920

Thr Leu  Asp Phe Pro Thr Gly  Thr Ser Gly Ser Pro  Ile Val Asp
    1925                 1930                 1935

Lys Asn  Gly Asp Val Ile Gly  Leu Tyr Gly Asn Gly  Val Ile Met
    1940                 1945                 1950

Pro Asn  Gly Ser Tyr Ile Ser  Ala Ile Val Gln Gly  Glu Arg Met
    1955                 1960                 1965

Asp Glu  Pro Ile Pro Ala Gly  Phe Glu Pro Glu Met  Leu Arg Lys
    1970                 1975                 1980

Lys Gln  Ile Thr Val Leu Asp  Leu His Pro Gly Ala  Gly Lys Thr
    1985                 1990                 1995

Arg Arg  Ile Leu Pro Gln Ile  Ile Lys Glu Ala Ile  Asn Arg Arg
    2000                 2005                 2010

Leu Arg  Thr Ala Val Leu Ala  Pro Thr Arg Val Val  Ala Ala Glu
    2015                 2020                 2025

Met Ala  Glu Ala Leu Arg Gly  Leu Pro Ile Arg Tyr  Gln Thr Ser
    2030                 2035                 2040

Ala Val  Pro Arg Glu His Asn  Gly Asn Glu Ile Val  Asp Val Met
    2045                 2050                 2055

Cys His  Ala Thr Leu Thr His  Arg Leu Met Ser Pro  His Arg Val
    2060                 2065                 2070

Pro Asn  Tyr Asn Leu Phe Val  Met Asp Glu Ala His  Phe Thr Asp
    2075                 2080                 2085

Pro Ala  Ser Ile Ala Ala Arg  Gly Tyr Ile Ser Thr  Lys Val Glu
    2090                 2095                 2100

Leu Gly  Glu Ala Ala Ala Ile  Phe Met Thr Ala Thr  Pro Pro Gly
    2105                 2110                 2115

Thr Ser  Asp Pro Phe Pro Glu  Ser Asn Ser Pro Ile  Ser Asp Leu
    2120                 2125                 2130

Gln Thr  Glu Ile Pro Asp Arg  Ala Trp Asn Ser Gly  Tyr Glu Trp
    2135                 2140                 2145

Ile Thr  Glu Tyr Thr Gly Lys  Thr Val Trp Phe Val  Pro Ser Val
    2150                 2155                 2160

Lys Met  Gly Asn Glu Ile Ala  Leu Cys Leu Gln Arg  Ala Gly Lys
    2165                 2170                 2175

Lys Val  Val Gln Leu Asn Arg  Lys Ser Tyr Glu Thr  Glu Tyr Pro
    2180                 2185                 2190

Lys Cys  Lys Asn Asp Asp Trp  Asp Phe Val Ile Thr  Thr Asp Ile
    2195                 2200                 2205

Ser Glu  Met Gly Ala Asn Phe  Lys Ala Ser Arg Val  Ile Asp Ser
    2210                 2215                 2220

Arg Lys  Ser Val Lys Pro Thr  Ile Ile Thr Glu Gly  Glu Gly Arg
```

```
    2225                2230                2235

Val Ile  Leu Gly Glu Pro Ser  Ala Val Thr Ala Ala  Ser Ala Ala
    2240                2245                2250

Gln Arg  Arg Gly Arg Ile Gly  Arg Asn Pro Ser Gln  Val Gly Asp
    2255                2260                2265

Glu Tyr  Cys Tyr Gly Gly His  Thr Asn Glu Asp Asp  Ser Asn Phe
    2270                2275                2280

Ala His  Trp Thr Glu Ala Arg  Ile Met Leu Asp Asn  Ile Asn Met
    2285                2290                2295

Pro Asn  Gly Leu Ile Ala Gln  Phe Tyr Gln Pro Glu  Arg Glu Lys
    2300                2305                2310

Val Tyr  Thr Met Asp Gly Glu  Tyr Arg Leu Arg Gly  Glu Glu Arg
    2315                2320                2325

Lys Asn  Phe Leu Glu Leu Leu  Arg Thr Ala Asp Leu  Pro Val Trp
    2330                2335                2340

Leu Ala  Tyr Lys Val Ala Ala  Ala Gly Val Ser Tyr  His Asp Arg
    2345                2350                2355

Arg Trp  Cys Phe Asp Gly Pro  Arg Thr Asn Thr Ile  Leu Glu Asp
    2360                2365                2370

Asn Asn  Glu Val Glu Val Ile  Thr Lys Leu Gly Glu  Arg Lys Ile
    2375                2380                2385

Leu Arg  Pro Arg Trp Ile Asp  Ala Arg Val Tyr Ser  Asp His Gln
    2390                2395                2400

Ala Leu  Lys Ala Phe Lys Asp  Phe Ala Ser Gly Lys  Arg Ser Gln
    2405                2410                2415

Ile Gly  Leu Ile Glu Val Leu  Gly Lys Met Pro Glu  His Phe Met
    2420                2425                2430

Gly Lys  Thr Trp Glu Ala Leu  Asp Thr Met Tyr Val  Val Ala Thr
    2435                2440                2445

Ala Glu  Lys Gly Gly Arg Ala  His Arg Met Ala Leu  Glu Glu Leu
    2450                2455                2460

Pro Asp  Ala Leu Gln Thr Ile  Ala Leu Ile Ala Leu  Leu Ser Val
    2465                2470                2475

Met Thr  Met Gly Val Phe Phe  Leu Leu Met Gln Arg  Lys Gly Ile
    2480                2485                2490

Gly Lys  Ile Gly Leu Gly Gly  Ala Val Leu Gly Val  Ala Thr Phe
    2495                2500                2505

Phe Cys  Trp Met Ala Glu Val  Pro Gly Thr Lys Ile  Ala Gly Met
    2510                2515                2520

Leu Leu  Leu Ser Leu Leu Leu  Met Ile Val Leu Ile  Pro Glu Pro
    2525                2530                2535

Glu Lys  Gln Arg Ser Gln Thr  Asp Asn Gln Leu Ala  Val Phe Leu
    2540                2545                2550

Ile Cys  Val Met Thr Leu Val  Ser Ala Val Ala Ala  Asn Glu Met
    2555                2560                2565

Gly Trp  Leu Asp Lys Thr Lys  Ser Asp Ile Ser Ser  Leu Phe Gly
    2570                2575                2580

Gln Arg  Ile Glu Val Lys Glu  Asn Phe Ser Met Gly  Glu Phe Leu
    2585                2590                2595

Leu Asp  Leu Arg Pro Ala Thr  Ala Trp Ser Leu Tyr  Ala Val Thr
    2600                2605                2610

Thr Ala  Val Leu Thr Pro Leu  Leu Lys His Leu Ile  Thr Ser Asp
    2615                2620                2625
```

```
Tyr Ile  Asn Thr Ser Leu Thr  Ser Ile Asn Val Gln  Ala Ser Ala
    2630                2635                2640

Leu Phe  Thr Leu Ala Arg Gly  Phe Pro Phe Val Asp  Val Gly Val
    2645                2650                2655

Ser Ala  Leu Leu Leu Ala Ala  Gly Cys Trp Gly Gln  Val Thr Leu
    2660                2665                2670

Thr Val  Thr Val Thr Ala Ala  Thr Leu Leu Phe Cys  His Tyr Ala
    2675                2680                2685

Tyr Met  Val Pro Gly Trp Gln  Ala Glu Ala Met Arg  Ser Ala Gln
    2690                2695                2700

Arg Arg  Thr Ala Ala Gly Ile  Met Lys Asn Ala Val  Val Asp Gly
    2705                2710                2715

Ile Val  Ala Thr Asp Val Pro  Glu Leu Glu Arg Thr  Thr Pro Ile
    2720                2725                2730

Met Gln  Lys Lys Val Gly Gln  Ile Met Leu Ile Leu  Val Ser Leu
    2735                2740                2745

Ala Ala  Val Val Val Asn Pro  Ser Val Lys Thr Val  Arg Glu Ala
    2750                2755                2760

Gly Ile  Leu Ile Thr Ala Ala  Ala Val Thr Leu Trp  Glu Asn Gly
    2765                2770                2775

Ala Ser  Ser Val Trp Asn Ala  Thr Thr Ala Ile Gly  Leu Cys His
    2780                2785                2790

Ile Met  Arg Gly Gly Trp Leu  Ser Cys Leu Ser Ile  Thr Trp Thr
    2795                2800                2805

Leu Ile  Lys Asn Met Glu Lys  Pro Gly Leu Lys Arg  Gly Gly Ala
    2810                2815                2820

Lys Gly  Arg Thr Leu Gly Glu  Val Trp Lys Glu Arg  Leu Asn Gln
    2825                2830                2835

Met Thr  Lys Glu Glu Phe Thr  Arg Tyr Arg Lys Glu  Ala Ile Ile
    2840                2845                2850

Glu Val  Asp Arg Ser Ala Ala  Lys His Ala Arg Lys  Glu Gly Asn
    2855                2860                2865

Val Thr  Gly Gly His Pro Val  Ser Arg Gly Thr Ala  Lys Leu Arg
    2870                2875                2880

Trp Leu  Val Glu Arg Arg Phe  Leu Glu Pro Val Gly  Lys Val Ile
    2885                2890                2895

Asp Leu  Gly Cys Gly Arg Gly  Gly Trp Cys Tyr Tyr  Met Ala Thr
    2900                2905                2910

Gln Lys  Arg Val Gln Glu Val  Arg Gly Tyr Thr Lys  Gly Gly Pro
    2915                2920                2925

Gly His  Glu Glu Pro Gln Leu  Val Gln Ser Tyr Gly  Trp Asn Ile
    2930                2935                2940

Val Thr  Met Lys Ser Gly Val  Asp Val Phe Tyr Arg  Pro Ser Glu
    2945                2950                2955

Cys Cys  Asp Thr Leu Leu Cys  Asp Ile Gly Glu Ser  Ser Ser Ser
    2960                2965                2970

Ala Glu  Val Glu Glu His Arg  Thr Ile Arg Val Leu  Glu Met Val
    2975                2980                2985

Glu Asp  Trp Leu His Arg Gly  Pro Arg Glu Phe Cys  Val Lys Val
    2990                2995                3000

Leu Cys  Pro Tyr Met Pro Lys  Val Ile Glu Lys Met  Glu Leu Leu
    3005                3010                3015
```

```
Gln Arg  Arg Tyr Gly Gly Gly  Leu Val Arg Asn Pro  Leu Ser Arg
    3020                 3025                 3030

Asn Ser  Thr His Glu Met Tyr  Trp Val Ser Arg Ala  Ser Gly Asn
    3035                 3040                 3045

Val Val  His Ser Val Asn Met  Thr Ser Gln Val Leu  Leu Gly Arg
    3050                 3055                 3060

Met Glu  Lys Arg Thr Trp Lys  Gly Pro Gln Tyr Glu  Glu Asp Val
    3065                 3070                 3075

Asn Leu  Gly Ser Gly Thr Arg  Ala Val Gly Lys Pro  Leu Leu Asn
    3080                 3085                 3090

Ser Asp  Thr Ser Lys Ile Lys  Asn Arg Ile Glu Arg  Leu Arg Arg
    3095                 3100                 3105

Glu Tyr  Ser Ser Thr Trp His  His Asp Glu Asn His  Pro Tyr Arg
    3110                 3115                 3120

Thr Trp  Asn Tyr His Gly Ser  Tyr Asp Val Lys Pro  Thr Gly Ser
    3125                 3130                 3135

Ala Ser  Ser Leu Val Asn Gly  Val Val Arg Leu Leu  Ser Lys Pro
    3140                 3145                 3150

Trp Asp  Thr Ile Thr Asn Val  Thr Thr Met Ala Met  Thr Asp Thr
    3155                 3160                 3165

Thr Pro  Phe Gly Gln Gln Arg  Val Phe Lys Glu Lys  Val Asp Thr
    3170                 3175                 3180

Lys Ala  Pro Glu Pro Pro Glu  Gly Val Lys Tyr Val  Leu Asn Glu
    3185                 3190                 3195

Thr Thr  Asn Trp Leu Trp Ala  Phe Leu Ala Arg Glu  Lys Arg Pro
    3200                 3205                 3210

Arg Met  Cys Ser Arg Glu Glu  Phe Ile Arg Lys Val  Asn Ser Asn
    3215                 3220                 3225

Ala Ala  Leu Gly Ala Met Phe  Glu Glu Gln Asn Gln  Trp Arg Ser
    3230                 3235                 3240

Ala Arg  Glu Ala Val Glu Asp  Pro Lys Phe Trp Glu  Met Val Asp
    3245                 3250                 3255

Glu Glu  Arg Glu Ala His Leu  Arg Gly Glu Cys His  Thr Cys Ile
    3260                 3265                 3270

Tyr Asn  Met Met Gly Lys Arg  Glu Lys Lys Pro Gly  Glu Phe Gly
    3275                 3280                 3285

Lys Ala  Lys Gly Ser Arg Ala  Ile Trp Phe Met Trp  Leu Gly Ala
    3290                 3295                 3300

Arg Phe  Leu Glu Phe Glu Ala  Leu Gly Phe Leu Asn  Glu Asp His
    3305                 3310                 3315

Trp Leu  Gly Arg Lys Asn Ser  Gly Gly Gly Val Glu  Gly Leu Gly
    3320                 3325                 3330

Leu Gln  Lys Leu Gly Tyr Ile  Leu Arg Glu Val Gly  Thr Arg Pro
    3335                 3340                 3345

Gly Gly  Lys Ile Tyr Ala Asp  Asp Thr Ala Gly Trp  Asp Thr Arg
    3350                 3355                 3360

Ile Thr  Arg Ala Asp Leu Glu  Asn Glu Ala Lys Val  Leu Glu Leu
    3365                 3370                 3375

Leu Asp  Gly Glu His Arg Arg  Leu Ala Arg Ala Ile  Ile Glu Leu
    3380                 3385                 3390

Thr Tyr  Arg His Lys Val Val  Lys Val Met Arg Pro  Ala Ala Asp
    3395                 3400                 3405

Gly Arg  Thr Val Met Asp Val  Ile Ser Arg Glu Asp  Gln Arg Gly
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    3410                3415                3420

Ser Gly  Gln Val Val Thr Tyr  Ala Leu Asn Thr Phe  Thr Asn Leu
    3425                3430                3435

Ala Val  Gln Leu Val Arg Met  Met Glu Gly Glu Gly  Val Ile Gly
    3440                3445                3450

Pro Asp  Asp Val Glu Lys Leu  Thr Lys Gly Lys Gly  Pro Lys Val
    3455                3460                3465

Arg Thr  Trp Leu Phe Glu Asn  Gly Glu Glu Arg Leu  Ser Arg Met
    3470                3475                3480

Ala Val  Ser Gly Asp Asp Cys  Val Val Lys Pro Leu  Asp Asp Arg
    3485                3490                3495

Phe Ala  Thr Ser Leu His Phe  Leu Asn Ala Met Ser  Lys Val Arg
    3500                3505                3510

Lys Asp  Ile Gln Glu Trp Lys  Pro Ser Thr Gly Trp  Tyr Asp Trp
    3515                3520                3525

Gln Gln  Val Pro Phe Cys Ser  Asn His Phe Thr Glu  Leu Ile Met
    3530                3535                3540

Lys Asp  Gly Arg Thr Leu Val  Val Pro Cys Arg Gly  Gln Asp Glu
    3545                3550                3555

Leu Val  Gly Arg Ala Arg Ile  Ser Pro Gly Ala Gly  Trp Asn Val
    3560                3565                3570

Arg Asp  Thr Ala Cys Leu Ala  Lys Ser Tyr Ala Gln  Met Trp Leu
    3575                3580                3585

Leu Leu  Tyr Phe His Arg Arg  Asp Leu Arg Leu Met  Ala Asn Ala
    3590                3595                3600

Ile Cys  Ser Ala Val Pro Val  Asn Trp Val Pro Thr  Gly Arg Thr
    3605                3610                3615

Thr Trp  Ser Ile His Ala Gly  Gly Glu Trp Met Thr  Thr Glu Asp
    3620                3625                3630

Met Leu  Glu Val Trp Asn Arg  Val Trp Ile Glu Glu  Asn Glu Trp
    3635                3640                3645

Met Glu  Asp Lys Thr Pro Val  Glu Lys Trp Ser Asp  Val Pro Tyr
    3650                3655                3660

Ser Gly  Lys Arg Glu Asp Ile  Trp Cys Gly Ser Leu  Ile Gly Thr
    3665                3670                3675

Arg Ala  Arg Ala Thr Trp Ala  Glu Asn Ile Gln Val  Ala Ile Asn
    3680                3685                3690

Gln Val  Arg Ala Ile Ile Gly  Asp Glu Lys Tyr Val  Asp Tyr Met
    3695                3700                3705

Ser Ser  Leu Lys Arg Tyr Glu  Asp Thr Thr Leu Val  Glu Asp Thr
    3710                3715                3720

Val Leu
    3725
```

The invention claimed is:

1. A nucleic acid chimera comprising:

a first nucleic acid molecule comprising a 5' non-coding region, a nucleic acid encoding a capsid (C) protein and non-structural proteins, and a 3' non-coding region, each from a West Nile virus genome, wherein the C protein comprises a portion of a premembrane (prM) signal sequence from the West Nile virus genome and a portion of a prM signal sequence from a Zika virus genome; and

a second nucleic acid molecule operably linked to the first nucleic acid molecule, encoding a prM protein and an envelope (E) protein from the Zika virus genome.

2. The nucleic acid chimera of claim 1, wherein:

(i) the portion of the prM signal sequence from the West Nile virus genome comprises the first 15 amino acids of the West Nile virus prM signal sequence and the portion of the prM signal sequence from the Zika virus genome comprises the last three amino acids of the Zika virus prM signal sequence;

(ii) the portion of the prM signal sequence from the West Nile virus genome comprises the first 13 amino acids of the West Nile virus prM signal sequence and the portion of the prM signal sequence from the Zika virus genome comprises the last five amino acids of the Zika virus prM signal sequence; or

(iii) the portion of the prM signal sequence from the West Nile virus genome comprises the first three amino acids of the West Nile virus prM signal sequence and the portion of the prM signal sequence from the Zika virus genome comprises the last 15 amino acids of the Zika virus prM signal sequence.

3. The nucleic acid chimera of claim **2**(i), wherein:

the first 15 amino acids of the West Nile virus prM signal sequence comprises amino acids 106-120 of SEQ ID NO: 2 or SEQ ID NO: 4;

the last three amino acids of the Zika virus prM signal sequence comprises AMA; or

the first 15 amino acids of the West Nile virus prM signal sequence comprises amino acids 106-120 of SEQ ID NO: 2 or SEQ ID NO: 4, and the last three amino acids of the Zika virus prM signal sequence comprises AMA.

4. The nucleic acid chimera of claim **2**(ii), wherein:

the first 13 amino acids of the West Nile virus prM signal sequence comprises amino acids 106-118 of SEQ ID NO: 6;

the last five amino acids of the Zika virus prM signal sequence comprises amino acids 119-123 of SEQ ID NO: 6; or

the first 13 amino acids of the West Nile virus prM signal sequence comprises amino acids 106-118 of SEQ ID NO: 6 and the last five amino acids of the Zika virus prM signal sequence comprises amino acids 119-123 of SEQ ID NO: 6.

5. The nucleic acid chimera of claim **2**(iii), wherein:

the first three amino acids of the West Nile virus prM signal sequence comprises amino acids 106-108 of SEQ ID NO: 8;

the last 15 amino acids of the Zika virus prM signal sequence comprises amino acids 109-123 of SEQ ID NO: 8; or

the first three amino acids of the West Nile virus prM signal sequence comprises amino acids 106-108 of SEQ ID NO: 8 and the last 15 amino acids of the Zika virus prM signal sequence comprises amino acids 109-123 of SEQ ID NO: 8.

6. The nucleic acid chimera of claim **1**, wherein the West Nile virus is strain NY99.

7. The nucleic acid chimera of claim **1**, wherein the Zika virus is strain SPH2015, PRVABC59 or R103451.

8. The nucleic acid chimera of claim **1**, comprising a nucleic acid sequence at least 95% identical to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7.

9. The nucleic acid chimera of claim **8**, comprising the nucleic acid sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7.

10. The nucleic acid chimera of claim **1**, wherein the nucleic acid chimera encodes an amino acid sequence at least 95% identical to SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8.

11. The nucleic acid chimera of claim **10**, wherein the nucleic acid chimera encodes the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8.

12. An immunogenic composition comprising an inactivated virus comprising the nucleic acid chimera of claim **1** and a pharmaceutically acceptable carrier.

13. The immunogenic composition of claim **12**, wherein the inactivated virus is inactivated by one or more of chemical treatment, physical treatment and irradiation.

14. A method of eliciting an immune response against Zika virus in a subject, comprising administering to the subject the immunogenic composition of claim **12**.

15. A method, comprising inactivating a virus comprising a nucleic acid chimera of claim **1**.

16. The method of claim **15**, wherein inactivating the virus comprises treating the virus with a chemical inactivation agent, high pressure, ultraviolet irradiation, gamma irradiation, or any combination thereof.

17. The method of claim **15**, further comprising administering the inactivated virus to a subject.

18. The nucleic acid chimera of claim **1**, further comprising a reporter gene.

19. The nucleic acid chimera of claim **18**, wherein the reporter gene encodes a fluorescent protein or a bioluminescent protein.

20. The nucleic acid chimera of claim **18**, wherein the reporter gene is human codon optimized.

21. The nucleic acid chimera of claim **18**, comprising a nucleic acid sequence at least 95% identical to SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 19.

22. The nucleic acid chimera of claim **21**, comprising the nucleic acid sequence of SEQ ID NO: 9, SEQ ID NO: 11 or SEQ ID NO: 19.

23. A chimeric virus, comprising the nucleic acid chimera of claim **18**.

24. A method of detecting Zika virus-specific antibodies in a sample, comprising:

contacting the sample with the chimeric virus of claim **23** under conditions sufficient to form virus-antibody complexes if Zika virus antibodies are present in the sample; and

detecting the virus-antibody complexes, thereby detecting Zika virus-specific antibodies in the sample.

25. A method of detecting Zika virus-specific antibodies in a sample, comprising:

contacting the sample with the chimeric virus of claim **23** to form a virus-sample mixture, wherein virus-antibody complexes are formed in the virus-sample mixture if Zika virus-specific antibodies are present in the sample;

inoculating a cell culture with the virus-sample mixture under conditions sufficient to allow plaque formation or micro-focus formation in the cell culture; and

detecting a decrease in plaque formation or micro-focus formation in the cell culture as compared to a control cell culture, thereby detecting a Zika virus-specific antibody in the sample.

26. A method of detecting Zika virus-specific antibodies in a sample, comprising:

providing the chimeric virus of claim **23** bound to a solid support;

contacting the chimeric virus-bound solid support with the sample under conditions sufficient to form virus-antibody complexes if Zika virus-specific antibodies are present in the sample;

contacting the virus-antibody complexes with a secondary antibody; and

detecting binding of the secondary antibody to the virus-antibody complexes, thereby detecting Zika virus-specific antibodies in the sample.

27. A method of detecting Zika virus-specific antibodies in a sample, comprising:

providing a secondary antibody bound to a solid support;

contacting the secondary antibody-bound solid support with the sample under conditions sufficient to allow binding of the secondary antibody to any Zika virus-specific antibodies present in the sample, thereby forming antibody-antibody complexes;

contacting the antibody-antibody complexes with the chimeric virus of claim **23** under conditions sufficient for the chimeric virus to bind the Zika virus-specific antibodies, thereby forming immune complexes; and

detecting the presence of the immune complexes, thereby detecting Zika virus-specific antibodies in the sample.

28. The method of claim **27**, wherein detecting the presence of the immune complexes comprises contacting the immune complexes with an antibody that specifically binds the chimeric virus and comprises a detectable label.

29. A method of detecting Zika virus-specific antibodies in a sample, comprising:

providing a Zika virus-specific antibody bound to a solid support;

contacting the antibody-bound solid support with the chimeric virus of claim **23** under conditions sufficient for the chimeric virus to bind the Zika virus-specific antibody to form antibody-virus complexes;

contacting the antibody-virus complexes with the sample to allow binding of any Zika virus-specific antibodies present in the sample to the chimeric virus, thereby forming immune complexes;

contacting the immune complexes with a secondary antibody; and

detecting binding of the secondary antibody to the immune complexes, thereby detecting Zika virus-specific antibodies present in the sample.

30. The method of claim **26**, wherein the secondary antibody comprises an anti-IgM antibody or an anti-IgG antibody.

31. The method of claim **24**, wherein the sample comprises a biological fluid sample.

32. The method of claim **31**, wherein the biological fluid sample comprises serum, blood or plasma.

33. A chimeric virus, comprising the nucleic acid chimera of claim **1**.

34. A method of detecting Zika virus-specific antibodies in a sample, comprising:

contacting the sample with the chimeric virus of claim **33** under conditions sufficient to form virus-antibody complexes if Zika virus antibodies are present in the sample; and

detecting the virus-antibody complexes, thereby detecting Zika virus-specific antibodies in the sample.

35. A method of detecting Zika virus-specific antibodies in a sample, comprising:

contacting the sample with the chimeric virus of claim **33** to form a virus-sample mixture, wherein virus-antibody complexes are formed in the virus-sample mixture if Zika virus-specific antibodies are present in the sample;

inoculating a cell culture with the virus-sample mixture under conditions sufficient to allow plaque formation or micro-focus formation in the cell culture; and

detecting a decrease in plaque formation or micro-focus formation in the cell culture as compared to a control cell culture, thereby detecting a Zika virus-specific antibody in the sample.

36. A method of detecting Zika virus-specific antibodies in a sample, comprising:

providing the chimeric virus of claim **33** bound to a solid support;

contacting the chimeric virus-bound solid support with the sample under conditions sufficient to form virus-antibody complexes if Zika virus-specific antibodies are present in the sample;

contacting the virus-antibody complexes with a secondary antibody; and

detecting binding of the secondary antibody to the virus-antibody complexes, thereby detecting Zika virus-specific antibodies in the sample.

37. A method of detecting Zika virus-specific antibodies in a sample, comprising:

providing a secondary antibody bound to a solid support;

contacting the secondary antibody-bound solid support with the sample under conditions sufficient to allow binding of the secondary antibody to any Zika virus-specific antibodies present in the sample, thereby forming antibody-antibody complexes;

contacting the antibody-antibody complexes with the chimeric virus of claim **33** under conditions sufficient for the chimeric virus to bind the Zika virus-specific antibodies, thereby forming immune complexes; and

detecting the presence of the immune complexes, thereby detecting Zika virus-specific antibodies in the sample.

38. The method of claim **37**, wherein detecting the presence of the immune complexes comprises contacting the immune complexes with an antibody that specifically binds the chimeric virus and comprises a detectable label.

39. A method of detecting Zika virus-specific antibodies in a sample, comprising:

providing a Zika virus-specific antibody bound to a solid support;

contacting the antibody-bound solid support with the chimeric virus of claim **33** under conditions sufficient for the chimeric virus to bind the Zika virus-specific antibody to form antibody-virus complexes;

contacting the antibody-virus complexes with the sample to allow binding of any Zika virus-specific antibodies present in the sample to the chimeric virus, thereby forming immune complexes;

contacting the immune complexes with a secondary antibody; and

detecting binding of the secondary antibody to the immune complexes, thereby detecting Zika virus-specific antibodies present in the sample.

* * * * *

专利名称(译)	嵌合西尼罗河/寨卡病毒及其使用方法		
公开(公告)号	US10632185	公开(公告)日	2020-04-28
申请号	US16/315897	申请日	2017-07-06
[标]申请(专利权)人(译)	美国卫生及公共服务部		
申请(专利权)人(译)	THE U.S.A.，为代表局局长，卫生与公众服务		
当前申请(专利权)人(译)	美利坚合众国为代表局局长，卫生与公众服务		
[标]发明人	KINNEY CLAIRE Y H		
发明人	KINNEY, CLAIRE Y. H.		
IPC分类号	A61K39/12 A61K39/00 C07K14/005 G01N33/533 A61K39/295 C12N7/00		
CPC分类号	C12N7/00 G01N33/533 A61K39/12 C07K14/005 Y02A50/392 A61K2039/525 A61K2039/53 A61K2039/5252 Y02A50/394 C12N2770/24141 A61K2039/5254 C12N2770/24134 C12N2770/24122 C12N2770/24144		
优先权	62/359807 2016-07-08 US		
其他公开文献	US20190298818A1		
外部链接	Espacenet		

摘要(译)

嵌合黄病毒，包括非编码区，非结构蛋白，衣壳蛋白（C）和来自西尼罗河病毒（WNV）的一部分前膜（prM）信号序列，以及一部分prM信号序列，prM 描述了寨卡病毒（VIKV）的蛋白和E蛋白。 还描述了在受试者中引起免疫应答，例如针对ZIKV的免疫应答的组合物和方法。 进一步描述了利用嵌合西尼罗河病毒/寨卡病毒的诊断检测方法。