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Kinney et al.

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(54) **CHIMERIC WEST NILE/DENGUE VIRUSES**

FOREIGN PATENT DOCUMENTS

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(51) **Int. Cl.**
A61K 39/295 (2006.01)
A61K 48/00 (2006.01)

(52) **U.S. Cl.**
USPC **424/202.1; 424/218.1**

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

The disclosure provides chimeric West Nile/Dengue viruses comprising non-coding regions, non-structural proteins, and a C protein from a West Nile virus and prM and E proteins from a Dengue virus. Also disclosed are methods of using the chimeric viruses in diagnosis of Dengue viral infection, assessment of candidate Dengue virus vaccine efficacy, and production of Dengue prM and E proteins.

22 Claims, 9 Drawing Sheets

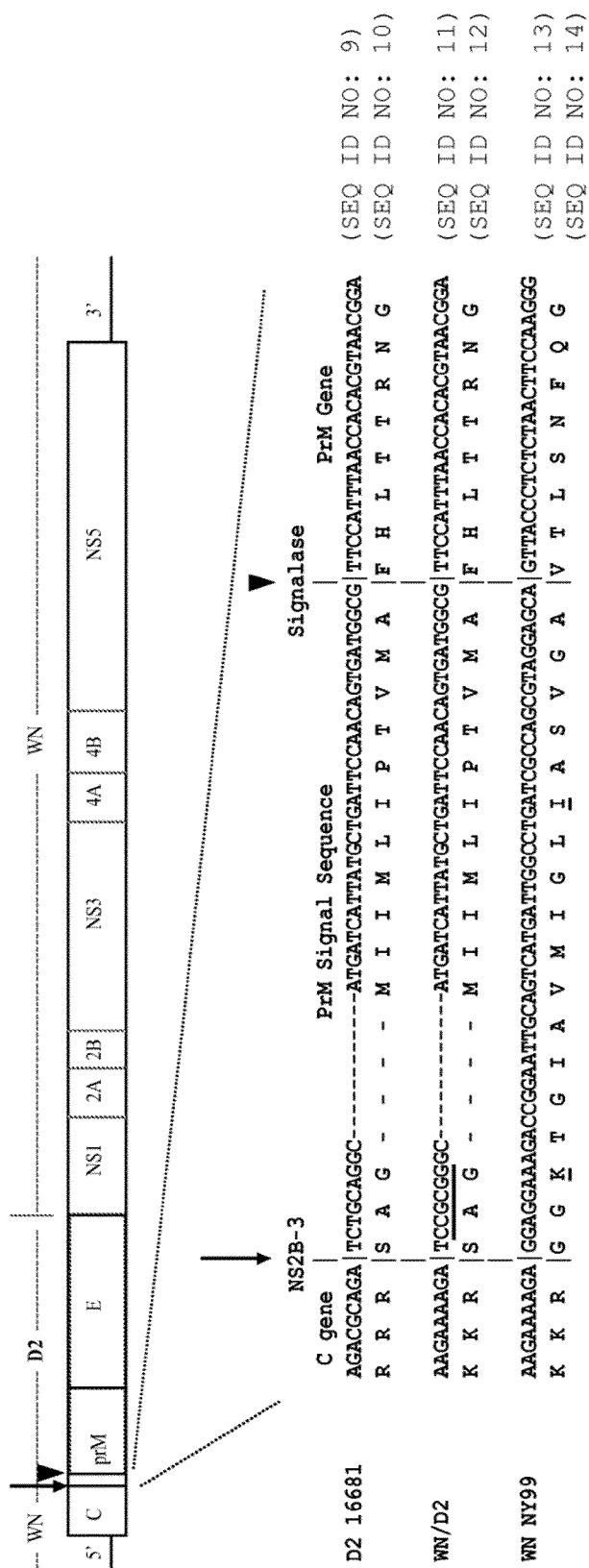


FIG. 1

FIG. 2A

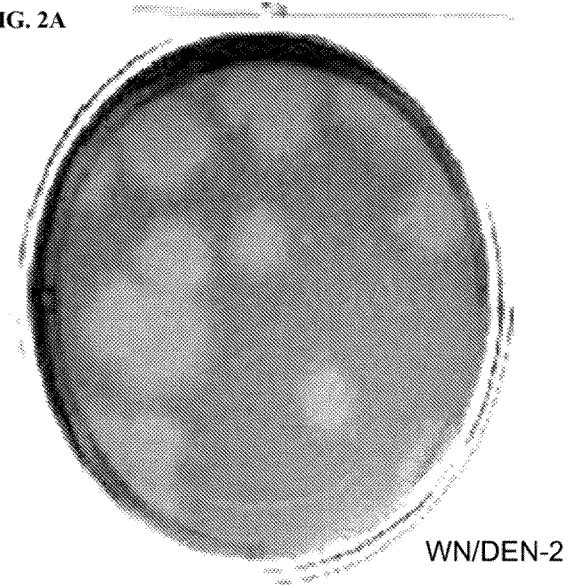


FIG. 2B

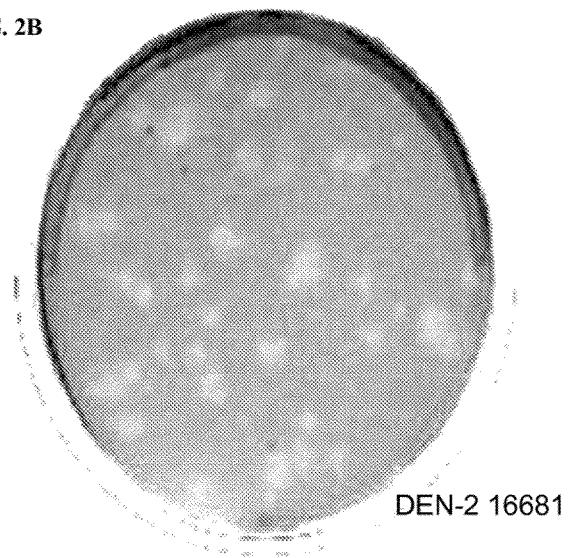


FIG. 3A

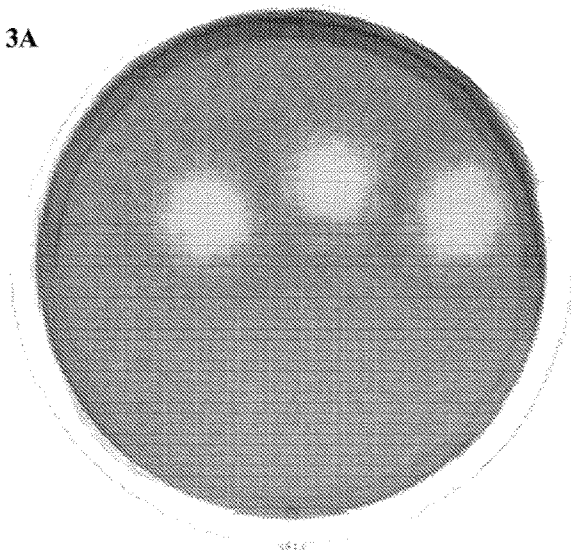


FIG. 3B

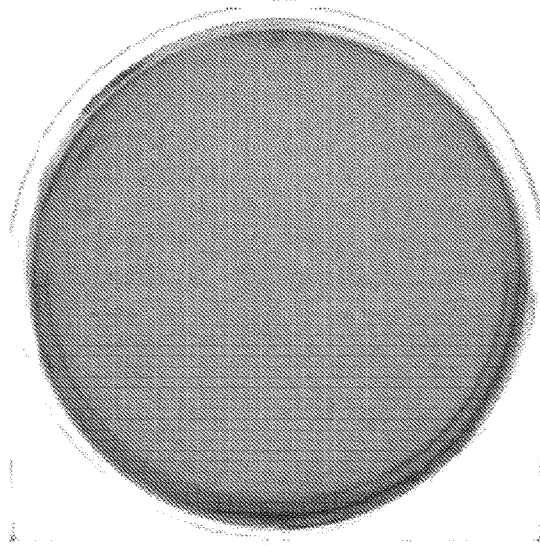


FIG. 3C

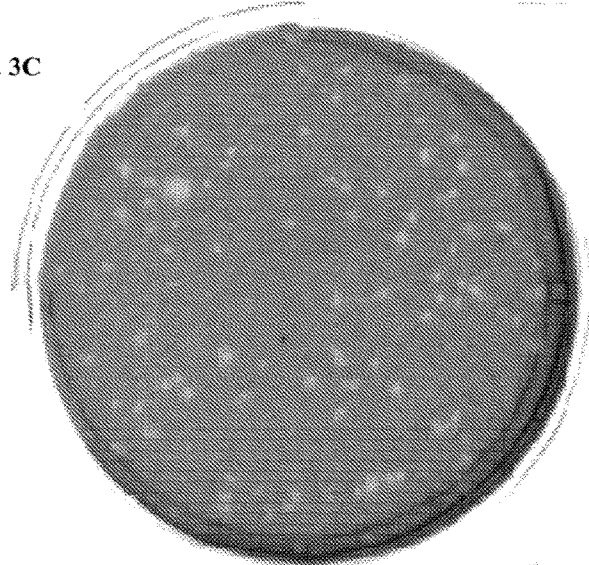


FIG. 3D

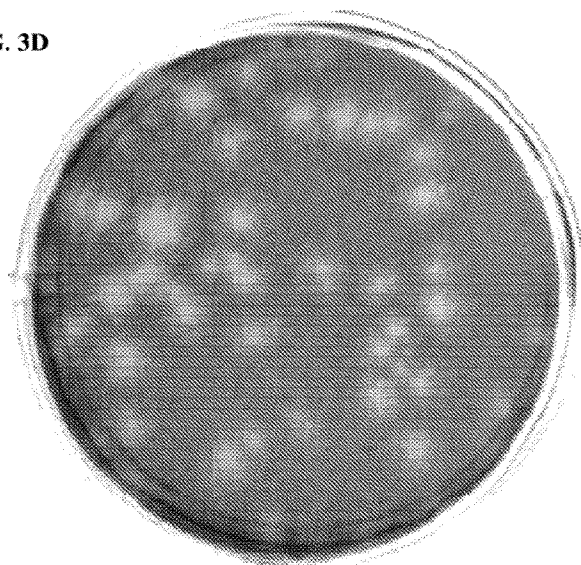


FIG. 3E

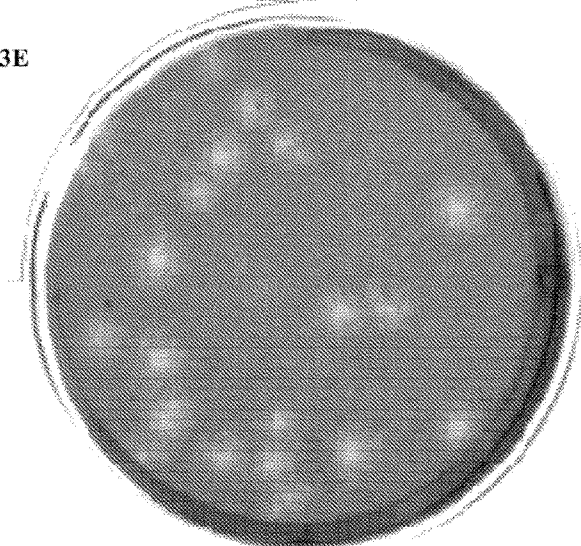
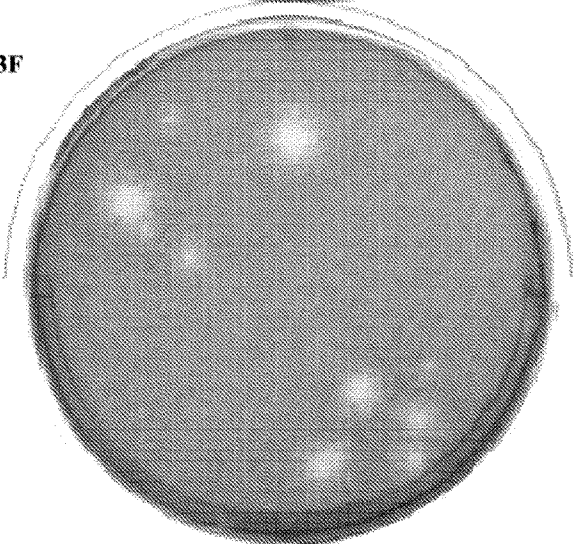


FIG. 3F



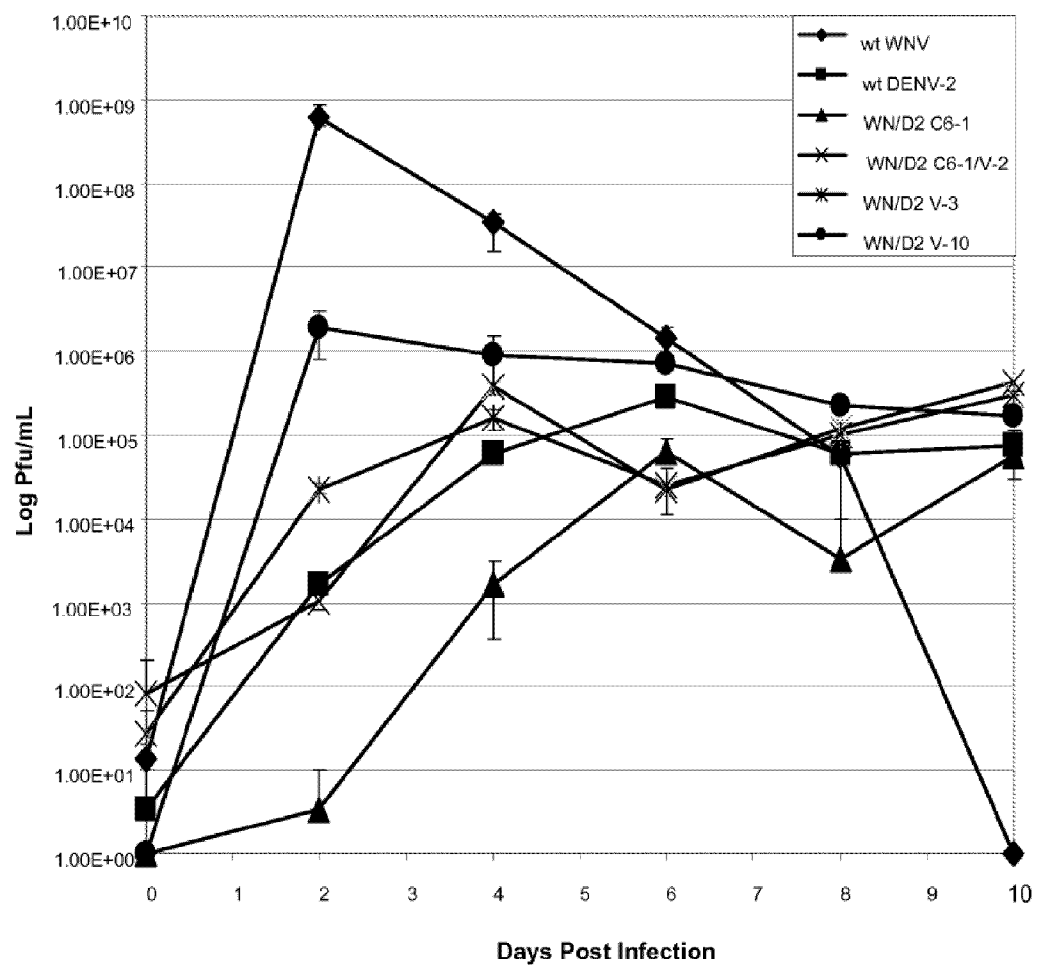


FIG. 4

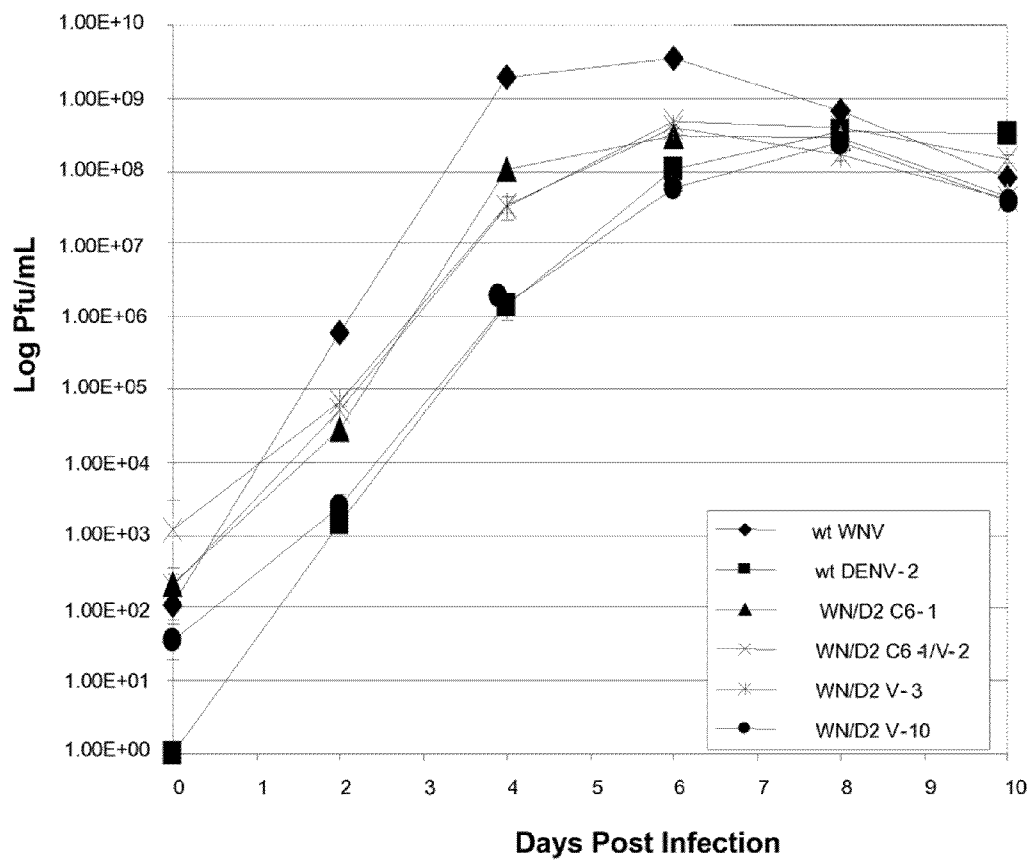


FIG. 5

FIG. 6A

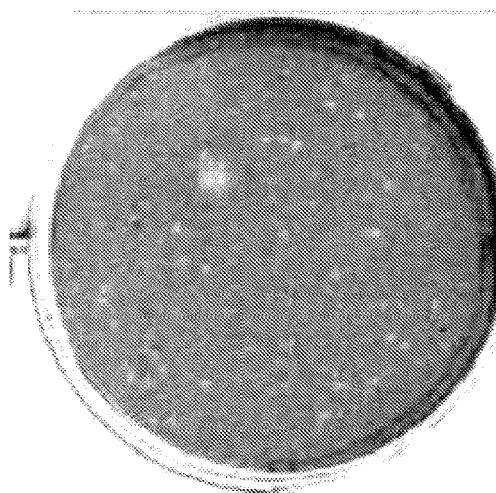


FIG. 6B

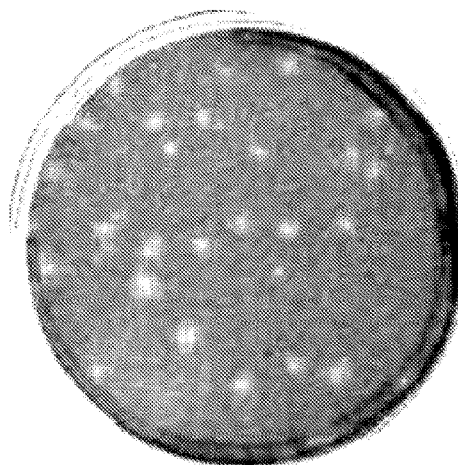


FIG. 6C

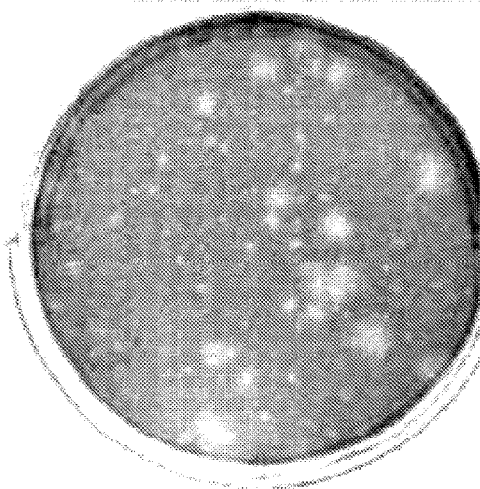
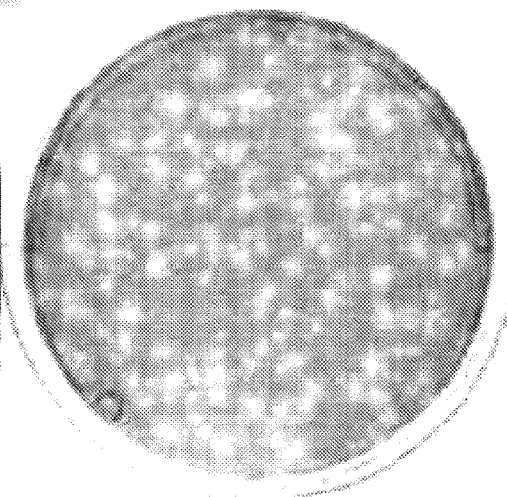


FIG. 6D



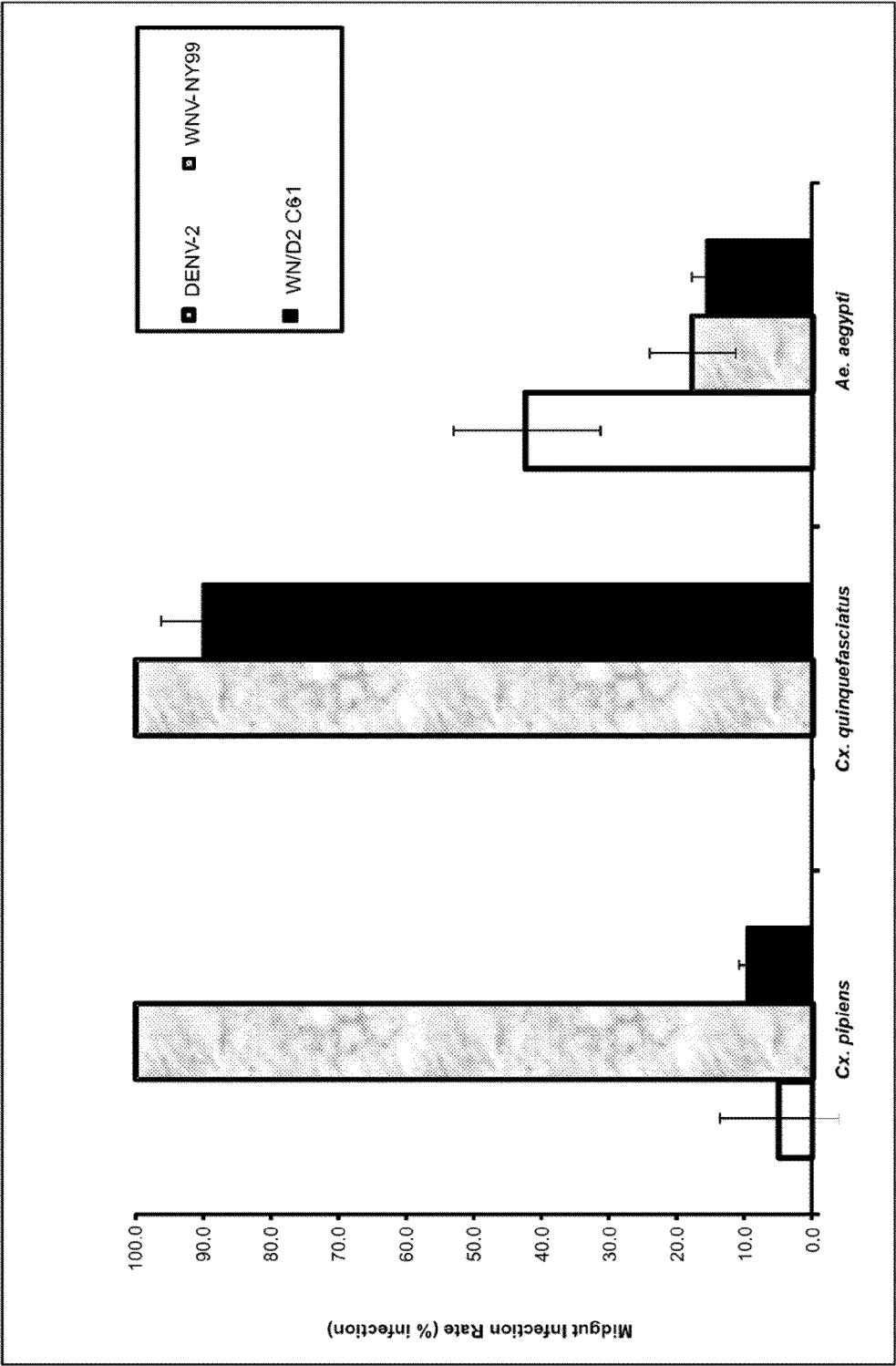
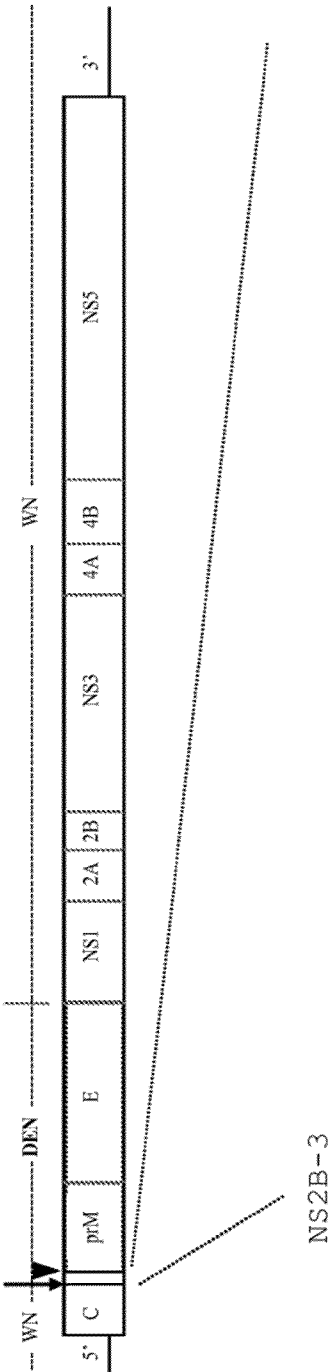


FIG. 7



C gene		PrM Signal Sequence		PrM Gene		Signalase	
WN/D1	AAGAAAAGA TCCGTGACC	-----ATGCTCCTTATGCTGCTGCCACAGCCCTGGCG	TTCCATCTGACGACACGAGGGGA	(SEQ ID NO: 15)	(SEQ ID NO: 16)		
	K K R S V T - - - - M L L M L L P T A L A F H L T T R G G						
WN/D3	AAGAAAAGA ACATCGCTC	-----TGCTCATGATGATGTTACAGCAACACTTGCT	TTCCACTTAACTTCACGAGATGGA	(SEQ ID NO: 17)	(SEQ ID NO: 18)		
	K K R T S L - - - - C L M M L P A T L A F H L T S R D G						
WN/D4	AAGAAAAGA TCAACGATA	-----ACATTGCTGTGCTTGATTCCACCCTAATGGCG	TTTCACCTTGTCACCAAGAGATGGC	(SEQ ID NO: 19)	(SEQ ID NO: 20)		
	K K R S T I - - - - T L L C L I P T V M A F H L S T R D G						

FIG. 8

1

CHIMERIC WEST NILE/DENGUE VIRUSES

CROSS REFERENCE TO RELATED APPLICATIONS

This is the §371 U.S. National Stage of International Application No. PCT/US2009/041824, filed Apr. 27, 2009, which was published in English under PCT Article 21(2), which in turn claims the benefit of U.S. Provisional Application No. 61/049,342, filed Apr. 30, 2008, which is incorporated by reference herein in its entirety.

FIELD

The disclosure relates to chimeric flaviviruses, particularly chimeric West Nile virus/Dengue virus constructs. Further, it relates to methods of using these chimeras in diagnosis of flavivirus infection and assessing candidate Dengue virus vaccine efficacy.

BACKGROUND

Dengue virus (DENV) is the most important arboviral cause of morbidity and mortality throughout the world. There are currently 2.5 billion people living in dengue endemic regions with roughly 100 million annual cases of dengue fever and hundreds of thousands of cases of dengue hemorrhagic fever and dengue shock syndrome (Gubler, *Clin. Microbiol. Rev.* 11:480-496, 1998). No vaccines are currently commercially available against any of the four DENV serotypes (DENV 1-4) largely because vaccine production is hampered by the fact that neutralizing antibodies to one serotype do not effectively neutralize the remaining DENV serotypes (Halstead and O'Rourke, *J. Exp. Med.* 146:201-217, 1977). In fact, low levels of these antibodies may actually increase the risk for more severe disease during secondary infection due to a phenomenon known as antibody mediated enhancement, which occurs when antibodies against one DENV serotype bind in a non-neutralizing manner to DENV particles of another serotype. This binding allows increased infection of Fc receptor-bearing cells, such as macrophages, which can change the infection profile of the virus or cause a release of chemokines leading to dengue hemorrhagic fever or dengue shock syndrome (Halstead and O'Rourke, *J. Exp. Med.* 146:201-217, 1977).

West Nile virus (WNV) is a member of the Japanese encephalitis serocomplex in the genus *Flavivirus*, family *Flaviviridae*. Until the mid-1990s, WNV caused sporadic outbreaks of illness in Africa, the Middle East, and Western Asia. However, since 1996, WN encephalitis has been reported more frequently in Europe, the Middle East, northern and western Africa, and Russia. WNV emerged in the western hemisphere in 1999 and has become the leading cause of arboviral encephalitis in humans and equines in North America. There are two lineages of WNV. Lineage 1, of which the NY99 strain is a member, is the more virulent strain and is the predominant strain infecting humans and horses (Jordan et al., *Viral Immunol.* 13:435-446, 2000). There is currently no approved vaccine for WNV to protect at-risk human populations from WN illness.

SUMMARY

Disclosed herein are chimeric flaviviruses including non-coding regions, non-structural proteins, and a C protein from WNV, and at least a portion of a prM protein and E protein from DENV. In some embodiments, the chimera includes a

2

first nucleic acid molecule including a 5' non-coding region, a nucleic acid encoding a C protein and non-structural proteins, and a 3' non-coding region from a West Nile virus and a second nucleic acid molecule operably linked to the first nucleic acid molecule, encoding at least a portion of a prM protein and E protein from a Dengue virus. In a particular example, the chimeric flavivirus includes nucleotide sequence(s) from DEN2 virus.

Also disclosed are chimeric flaviviruses including non-coding regions and non-structural proteins from WNV and at least a portion of a C protein, prM protein, and E protein from DENV. In some embodiments, the chimera includes a first nucleic acid molecule including a 5' non-coding region, a nucleic acid encoding non-structural proteins, and a 3' non-coding region from a WNV and a second nucleic acid molecule operably linked to the first nucleic acid molecule, encoding at least a portion of a C protein, a prM protein, and an E protein from a DENV.

In some examples, the chimeric flavivirus includes at least one nucleic acid or amino acid substitution which improves chimera characteristics (such as increased replication in cell culture or decreased infectivity or transmissibility in mosquitoes). In particular examples, the amino acid substitution is in the DENV prM protein, DENV E protein, WNV NS2A protein, or WNV NS4B protein. In additional examples, the chimeric flavivirus includes at least one nucleotide substitution in the 5' or 3' non-coding region.

In further examples, the chimeric flavivirus includes at least one amino acid substitution in the DENV E protein, wherein the substituted E protein exhibits measurably reduced antibody cross-reactivity.

Also disclosed herein are methods of using the chimeric flaviviruses in diagnosis of flavivirus infection. In a particular embodiment, the method includes detecting Dengue virus antibody in a sample, including contacting a sample from a subject with a chimeric flavivirus disclosed herein and detecting formation of an antibody-virus complex. In some embodiments methods of use of the chimeric flavivirus to evaluate efficacy of candidate Dengue virus vaccines are disclosed. Also disclosed are methods of producing Dengue virus structural proteins utilizing the chimeric flaviviruses described herein.

The foregoing and other features 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 is a schematic diagram of a WN/DEN2 chimeric flavivirus. The chimera contains the prM signal sequence (between the NS2B-3 protease and signalase cleavage sites, arrow and triangle, respectively), prM, and E proteins of the DEN2 16681 virus in the WN NY99 virus backbone. The enlarged sequence alignment shows the SacII restriction site (underlined) that was introduced in the cDNA clone to create the splice site to engineer the chimera. The mutations introduced to create the SacII site do not change the DEN2 amino acid sequence.

FIGS. 2A and 2B show the plaque phenotype of virus seed recovered from C6/36 cells. The amplified virus seed was plated on Vero cells to visualize plaques. FIG. 2A shows plaques formed by the chimeric WN/DEN2 virus on day 8 post-infection (p.i.). FIG. 2B shows plaques formed by DEN2 16681 virus on day 8 p.i.

FIGS. 3A to 3F show the plaque phenotype of virus recovered from C6/36 cells or Vero cells on day 5 p.i. at the

3

indicated passages. (A) wild type WNV NY99 (LLC-MK2-1); (B) wild type DEN2 16681 (C6-1); (C) WN/DEN2 (C6-1); (D) WN/DEN2 (C6-1/V-2); (E) WN/DEN2 (V-3); (F) WN/DEN2 (V-10).

FIG. 4 shows growth curves in Vero cells of the wild type WNV NY99 (wt WNV), wild type DEN2 16681 virus (wt DENV-2), and successive passages of WN/DEN2 seeds (WN/DEN2 C6-1 seed, C6-1/V-2 seed, V-3 seed, and V-10 seed). Each point represents an average titer from three flasks, with the error bars showing the highest and lowest titers at each time point. ♦, wild type WNV; ■, wild type DEN2; ▲, WN/DEN2; C6-1 seed; x, WN/DEN2 C6-1/V-2 seed; *, WN/DEN2 V-3 seed; ●, WN/DEN2 V-10 seed.

FIG. 5 shows growth curves in C6/36 cells of the wild type WNV NY99 (wt WNV), wild type DEN2 16681 virus (wt DENV-2), and successive passages of WN/DEN2 seeds (WN/DEN2 C6-1 seed, C6-1/V-2 seed, V-3 seed, and V-10 seed). ♦, wild type WNV; ■, wild type DEN2; ▲, WN/DEN2; C6-1 seed; x, WN/DEN2 C6-1/V-2 seed; *, WN/DEN2 V-3 seed; ●, WN/DEN2 V-10 seed.

FIGS. 6A to 6D show plaque phenotype of WN/DEN2 chimeras engineered to include E-203, NS2A49, and/or NS2A94 mutants. (A) WN/DEN2 C6-1 seed; (B) WN/DEN2 E-N203D V-1 seed; (C) WN/DEN2 NS2A-I49T/F94L V-1 seed; (D) WN/DEN2 N203D, NS2A-I49T/F94L V-1 seed.

FIG. 7 shows the midgut infection rate of wild type WNV-NY99, wild type DENV-2 16681, and WN/DEN2 C6-1 seed in *Culex pipiens*, *Culex quinquefasciatus*, and *Aedes aegypti* mosquitoes. Open bars, DENV-2; shaded bars, WNV-NY99; solid bars, WN/D2 C6-1 seed.

FIG. 8 is a schematic diagram of a WN/DEN chimeric flavivirus. The chimera contains the prM signal sequence from the indicated DEN virus (between the NS2B-3 protease and signalase cleavage sites, arrow and triangle, respectively), and prM and E proteins of the DEN virus in the WN NY99 virus backbone. The enlarged sequence alignment shows junction between the WNV C protein and the DENV prM signal sequence in the WN/DEN1, WN/DEN3, and WN/DEN4 chimeras.

SEQUENCE LISTING

Any nucleic acid and amino acid sequences listed herein or 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. In at least some cases, 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 in the form of the file named Sequence_Listing.txt, which was created on Oct. 22, 2010, and is 339,010 bytes, which is incorporated by reference herein.

SEQ ID NOs: 1 and 2 show the nucleic acid and amino acid sequences, respectively, of a recombinant West Nile/Dengue-2 chimera WN/DEN2. The start and stop positions of the particular genes and proteins of the chimera are shown in Table 1.

SEQ ID NOs: 3 and 4 show the nucleic acid and amino acid sequences, respectively, of a recombinant West Nile/Dengue-1 chimera. The start and stop positions of the particular genes and proteins of this chimera are shown in Table 1.

SEQ ID NOs: 5 and 6 show the nucleic acid and amino acid sequences, respectively, of a recombinant West Nile/Dengue-3 chimera. The start and stop positions of the particular genes and proteins of the chimera are shown in Table 2.

4

SEQ ID NOs: 7 and 8 show the nucleic acid and amino acid sequences, respectively, of a recombinant West Nile/Dengue-4 chimera. The start and stop positions of the particular genes and proteins of this chimera are shown in Table 1.

TABLE 1

Start and stop positions of NCRs, structural proteins and nonstructural proteins in WN/DEN2, WN/DEN1, and WN/DEN4 chimeras		
Region	Nucleotide start/stop position (SEQ ID NOs: 1, 3, and 7)	Amino acid start/stop position (SEQ ID NOs: 2, 4, and 8)
5' NCR	1-96	—
C	97-453	1-119
prM	454-951	120-285
M	727-951	211-285
E	952-2436	286-780
NS1	2437-3492	781-1132
NS2A	3493-4185	1133-1363
NS2B	4186-4578	1364-1494
NS3	4579-6435	1495-2113
NS4A	6436-6882	2114-2262
NS4B	6883-7647	2263-2517
NS5	7648-10362	2518-3422
3' NCR	10363-10996	—

TABLE 2

Start and stop positions of NCRs, structural proteins and nonstructural proteins in SEQ ID NOs: 5 and 6. (WN/DEN3 chimera)		
Region	Nucleotide start/stop position (SEQ ID NO: 5)	Amino acid start/stop position (SEQ ID NO: 6)
5' NCR	1-96	—
C	97-453	1-119
prM	454-951	120-285
M	727-951	211-285
E	952-2430	286-778
NS1	2431-3486	779-1130
NS2A	3487-4179	1131-1361
NS2B	4180-4572	1362-1492
NS3	4573-6429	1493-2111
NS4A	6430-6876	2113-2260
NS4B	6877-7641	2261-2515
NS5	7642-10356	2516-3420
3' NCR	10357-10990	—

SEQ ID NOs: 9 and 10 show the nucleic acid and amino acid sequences, respectively, of the C protein/prM junction in a wild type DEN2 16681 virus.

SEQ ID NOs: 11 and 12 show the nucleic acid and amino acid sequences, respectively, of the WN/DEN2 chimeric virus.

SEQ ID NOs: 13 and 14 show the nucleic acid and amino acid sequences, respectively, of the C protein/prM junction in a wild type WN NY99 virus.

SEQ ID NOs: 15 and 16 show the nucleic acid and amino acid sequences, respectively, of the WN/DENT chimeric virus.

SEQ ID NOs: 17 and 18 show the nucleic acid and amino acid sequences, respectively, of the WN/DEN3 chimeric virus.

SEQ ID NOs: 19 and 20 show the nucleic acid and amino acid sequences, respectively, of the WN/DEN4 chimeric virus.

DETAILED DESCRIPTION

Lack of an ideal DEN animal model is a major obstacle in vaccine and therapeutic development for DENV. Immuno-competent outbred mice do not succumb to wild type DENV

infection, so typical markers of protection, such as lethality and viremia, are not evident in mice after wild type DENV challenge. Transgenic and inbred mice have been used for DENV mouse models, but these animals are usually high cost, difficult to work with, and are not realistic for high-throughput or multiple dose experiments. Many animals are susceptible to WNV infection, and outbred mice, such as Swiss Webster and NIH Swiss, succumb to wild type WNV infection. Sickness, lethality, and viremia level have been successfully used as protection markers in WNV research using small animal models such as, mice, hamsters, and birds. Thus, chimeric WN/DEN viruses disclosed herein may be virulent and/or generate significant viremia in mice, therefore they can be used as the challenge dose to assess the efficacy of DENV candidate vaccines.

In addition, although both DENV and WNV are flaviviruses, DENV replicates much more slowly and to lower titers than WNV in cell cultures. This makes development of diagnostic viral antigen production and diagnostic tests for DENV more difficult than for WNV. The chimeric WN/DEN viruses described herein contain DENV antigenic structures on the surface of the virus particles while retaining certain WNV replication features (such as replication to high titer). The disclosed chimeras can thus be used as a DEN-like surrogate virus for testing DENV candidate vaccine efficacy and for development of faster or more effective DENV diagnostics.

I. Abbreviations

DEN: Dengue
 DENV: Dengue virus
 E: envelope glycoprotein
 ELISA: enzyme-linked immunosorbent assay
 HMAF: hyperimmune mouse ascitic fluid
 IFA: immunofluorescence antibody assay
 mAb: monoclonal antibody
 MOI: multiplicity of infection
 NCR: non-coding region
 pfu: plaque forming unit
 p.i.: post-infection
 prM: premembrane protein
 PRNT: plaque reduction neutralization test
 VD₅₀: 50% virulent dose
 WN: West Nile
 WNV: West Nile virus
 WN/DEN: West Nile/Dengue virus chimera

II. Terms

Unless otherwise noted, technical terms are used according to conventional usage. Definitions of common terms in molecular biology may be found in Benjamin Lewin, *Genes V*, published by Oxford University Press, 1994 (ISBN 0-19-854287-9); Kendrew et al. (eds.), *The Encyclopedia of Molecular Biology*, published by Blackwell Science Ltd., 1994 (ISBN 0-632-02182-9); and Robert A. Meyers (ed.), *Molecular Biology and Biotechnology: a Comprehensive Desk Reference*, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8).

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

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. Antibody binding affinity is substantially lowered (or measurably reduced) by the modification and/or substitution of one or more amino acids in the epitope recognized by the antibody paratope if the end-point titer of a specific antibody for the modified/substituted epitope differs by at least 4-fold, such as at least 10-fold, at least 100-fold or greater, as compared to the unaltered epitope.

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.

Chimera: A molecule (e.g., gene, transcript or protein) composed of parts that are of different origin (such as at least two nucleic acid or amino acid sequences) that, while typically unjoined in their native state, are joined or linked to form a single continuous molecule. A chimera may include nucleotide or amino acid sequences 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 acid sequences from more than one protein. A chimera may also include a chimeric nucleic acid sequence 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 Dengue virus. In some examples, a chimeric flavivirus includes nucleic acid sequences encoding one or more proteins from a first flavivirus and nucleic acid sequences encoding one or more proteins from a second flavivirus. In particular examples, a chimeric flavivirus is composed of a nucleotide sequence encoding the non-structural proteins and a C protein from a West Nile virus genome linked to a nucleotide sequence encoding at least a portion of a prM protein and E protein from a Dengue virus genome (such as DENT, DEN2, DEN3, or DEN4).

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 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 ability to replicate (for example as described in Example 2), by producing virus containing a variant protein and determining its neurovirulence or neuroinvasion properties (as described in Example 6), or by testing antibody cross-reactivity (as described in Example 10).

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 cross-reactive antibody: An antibody that recognizes (that is, specifically binds to) an epitope found on a peptide from more than one species of flavivirus. Flavivirus cross-reactive antibodies are classified as either complex cross-reactive or group cross-reactive antibodies. Complex cross-reactive antibodies recognize epitopes shared by all viruses within a complex, such as the JE virus complex or the DEN virus complex. Group cross-reactive antibodies recognize epitopes shared by all members of the genus Flavivirus.

Antibody cross-reactivity is further refined within the sub-complex and sub-group cross-reactive categories. Sub-complex cross-reactive antibodies recognize epitopes shared by most, but not all, members of a particular flavivirus complex (e.g., DEN-1, -2, and -3, but not DEN-4), while sub-group cross-reactive antibodies recognize epitopes shared by flaviviruses from several complexes, but not all members of the flavivirus group (e.g., all members of the DEN virus and JE virus complexes, but not all members of the tick-borne virus complex). Specific, non-limiting examples of flavivirus cross-reactive antibodies include the group cross-reactive mAbs 4G2 and 6B6C-1, the sub-group cross-reactive mAb 1B7-5, and the sub-complex cross-reactive mAb 10A1D-2. (see, e.g., Roehrig et al., *Virology* 246:317-28, 1998; Crill and Chang, *J. Virol.* 78:13975-13986, 2004).

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. NS 1 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, with the function of NS2A remaining unknown. 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 func-

tions 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).

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.

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 biological components in the cell of the organism in which the component naturally 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.

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.

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).

Recombinant nucleic acid: A nucleic acid molecule 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, 2nd ed., vol. 1-3, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of a natural nucleic acid molecule.

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. Appl. 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.

Orthologs (equivalent to proteins of other species) of proteins are in some instances characterized by possession of greater than 75% sequence identity counted over the full-length alignment with the amino acid sequence of specific protein using ALIGN set to default parameters. Proteins with even greater similarity to a reference sequence will show increasing percentage identities when assessed by this method, such as at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 98%, or at least 99% sequence identity. In addition, sequence identity can be compared over the full length of one or both binding domains of the disclosed fusion proteins.

When significantly less than the entire sequence is being compared for sequence identity, homologous sequences will typically possess at least 80% sequence identity over short windows of 10-20, and may possess sequence identities of at least 85%, at least 90%, at least 95%, 96%, 97%, 98%, or at least 99% depending on their similarity to the reference sequence. Sequence identity over such short windows can be

determined using LFASTA; methods are described at the NCBI website. One of skill in the art will appreciate that these sequence identity ranges are provided for guidance only; it is entirely possible that strongly significant homologs could be obtained that fall outside of the ranges provided. Similar homology concepts apply for nucleic acids as are described for protein. An alternative indication that two nucleic acid molecules are closely related is that the two molecules hybridize to each other under stringent conditions.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences, due to the degeneracy of the genetic code. It is understood that changes in nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that each encode substantially the same protein.

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).

Transformed: A "transformed" cell is a cell into which has been introduced a nucleic acid molecule 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, amelioration, or treatment of infectious or other types of disease. The immunogenic material may include attenuated or killed microorganisms (such as bacteria or viruses), or antigenic proteins, peptides or DNA derived from them. An attenuated vaccine 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. A killed vaccine is a previously virulent microorganism that has been killed with chemicals or heat, but elicits antibodies against the virulent microorganism. Vaccines may elicit both prophylactic (preventative) 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.

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 or amino acid sizes, 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.

III. WN/DEN Chimeric Viruses

Disclosed herein are chimeric flaviviruses that include non-coding regions, non-structural proteins, and a C protein from WNV, and at least a portion of a prM protein and E protein from DENV. In some embodiments, the chimera includes a first nucleic acid molecule including a 5' non-coding region, a nucleic acid encoding a C protein and non-structural proteins, and a 3' non-coding region from a West Nile virus genome and a second nucleic acid molecule operably linked to the first nucleic acid molecule, encoding at least a portion of a prM protein and E protein from a Dengue virus genome. In particular examples, the nucleic acid molecules encoding the prM and E proteins of the WNV genome are replaced with molecules having the corresponding sequences from the DENV genome. In some examples, the prM signal sequence of the WNV C protein is also replaced with the prM signal sequence of the corresponding DENV genome.

Also disclosed are chimeric flaviviruses including non-coding regions and non-structural proteins from WNV and at least a portion of a C protein, prM protein, and E protein from DENV. In some embodiments, the chimera includes a first nucleic acid molecule including a 5' non-coding region, a nucleic acid encoding non-structural proteins, and a 3' non-coding region from a WNV genome and a second nucleic acid molecule operably linked to the first nucleic acid molecule, encoding at least a portion of a C protein, a prM protein, and an E protein from a DENV genome. In a particular example, the nucleic acid encoding the C, prM, and E proteins of the WNV genome are replaced with molecules having the corresponding sequences from the DENV genome.

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/IC-P991 (such as GenBank Accession No. AF196835 (incorporated by reference as included in GenBank on Apr. 27, 2009) or with mutations as described in Kinney et al., *J. Gen. Virol.* 87:3611-3622, 2006).

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 Apr. 27, 2009. In further examples, the WNV genome, or the non-coding regions, non-structural proteins, and/or C protein of the WNV genome are 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 flavivirus chimeras, the DENV genome is from a Dengue 1 (DEN1), Dengue 2 (DEN2), Dengue 3 (DEN3), or Dengue 4 (DEN4) virus. In some examples, the DENV genome portion of the disclosed chimeras includes sequences from a single DENV genome, while in other examples, the DENV genome portion includes sequences from two or more DENV genomes. The DENV genome may be a wild type strain or an attenuated (or vaccine) strain. In some examples, the DENV genome is DEN2 (for example, wild type DEN2 16681 strain or attenuated DEN-2 PDK-53 strain), DEN1 (for example, wild type DEN1 16007 strain or attenuated DEN1 PDK-13 strain), DEN3 (for example, wild type DEN3 16562 strain or attenuated DEN3 PGMK-30/

13

FRhL-3) or DEN4 (for example, wild type DEN4 1036 or attenuated DEN4 PDK-48). Additional DENV strains are known in the art (see e.g., U.S. Pat. Nos. 5,939,254 and 6,793,488). In particular examples, the DENV genome is a wild type (non-attenuated) strain, for example DEN2 16681 (such as GenBank Accession No. U87411, incorporated by reference as included in GenBank on Apr. 27, 2009).

DENV sequences are publicly available. For example GenBank Accession Nos.: NC_001477, AF180817, and U88536 disclose DEN1 nucleic acid sequences; NC_001474 and U87411 disclose DEN2 nucleic acid sequences; NC_001475, AY099336, and AF317645 disclose DEN3 nucleic acid sequences; and NC_002640 and AF326825 disclose DEN4 nucleic acid sequences, all of which are incorporated by reference as included in GenBank on Apr. 27, 2009. In additional examples, the DENV genome (or the prM and/or E protein from the DENV genome) are at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a publicly available DENV sequence.

In a particular embodiment, the chimeric flavivirus includes a nucleic acid molecule having a sequence including the 5' and 3' non-coding regions of the virus and encoding the non-structural proteins and C protein from a WN NY99 virus genome, operably linked to a nucleic acid molecule having a sequence encoding the prM signal sequence, the prM protein and the E protein from DEN2 16681 virus genome. In one example, the chimeric flavivirus is a WN/DEN2 chimera having the nucleic acid and amino acid sequence shown in SEQ ID NOs: 1 and 2, respectively. In additional examples, the disclosed chimeric virus has nucleic acid and amino acid sequences at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical or more to the sequences disclosed in SEQ ID NOs: 1 and 2.

In other embodiments, the chimeric flaviviruses disclosed herein include a first nucleic acid molecule including the 5' and 3' non-coding regions and encoding the non-structural proteins and C protein from a WN NY99 virus genome operably linked to a second nucleic acid molecule encoding the prM and E proteins from a DEN1, DEN3, or DEN4 virus genome. In some examples, the second nucleic acid molecule encodes the prM signal sequence from a DEN1, DEN3, or DEN4 virus genome. Particular examples of WN/DEN1 (SEQ ID NOs: 3 and 4), WN/DEN3 (SEQ ID NOs: 5 and 6) and WN/DEN4 (SEQ ID NOs: 7 and 8) chimeras are disclosed herein. In additional examples, the disclosed chimeric viruses are at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical or more to the sequences disclosed in SEQ ID NOs: 3-8.

The disclosed chimeric flaviviruses 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 preferably 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. Preferably, cells are 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 can be adapted to growth in low serum or serum-free medium. 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

14

(human), HepG2 (human), and PDK (dog). Suitable cell lines can be obtained from the American Type Culture Collection (ATCC), Manassas, Va.

In some examples, the disclosed chimeric WN/DEN viruses replicate in cell culture more rapidly than DEN viruses. For example, plaques formed by WN/DEN chimeric viruses may form on cell cultures (such as C6/36 or Vero cells) sooner than DEN viruses (such as at least one day, two days, three days, four days, or five days post-infection sooner). In other examples, WN/DEN chimeric viruses may form larger plaques than DEN viruses. For example, plaques formed by chimeric WN/DEN viruses disclosed herein may form plaques that are at least 25% larger to about 10 times larger than DEN viruses (such as at least 50% larger, two-fold, three-fold, four-fold, five-fold, or up to 10-fold larger).
IV. WN/DEN Chimeras and Variants Thereof

The disclosure also provides flavivirus chimeras having one or more nucleic acid or amino acid substitution, insertion, deletion, or combination thereof, such that the resulting chimera has improved characteristics. In some examples, the improved characteristic of the chimera including one or more substitution, insertion, and/or deletion 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 comprising one or more substitution, insertion, and/or deletion, 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.

Manipulation of the nucleotide sequence of the disclosed chimeric flaviviruses using 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*, 2nd 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

-continued

Original Residue	Conservative Substitutions
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; (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 aspartyl; 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.

In addition to targeted mutagenesis to produce variants of the disclosed WN/DENV chimeras, naturally occurring mutations may accrue upon passage in cell culture that result in variants, some with desirable characteristics. Nucleic acid and amino acid substitutions, insertions, 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/DENV 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 (Huang et al., *J. Virol.* 77:11436-11447, 2003; Huang et al., *J. Virol.* 12:7300-7310, 2005).

In some embodiments, the chimeric flavivirus encodes a polypeptide that includes one or more amino acid substitution (or insertion or deletion) of one or more residues of the Dengue virus prM or E protein, such that the chimera has improved characteristics. In other examples, the chimeric flavivirus encodes a polypeptide that includes one or more amino acid substitution (or insertion or deletion) of one or more residues of a WNV non-structural and/or C protein, such that the resulting chimera has improved characteristics. In additional examples, the chimeric flavivirus includes one or more nucleic acid substitution, insertion, or deletion in the WNV 5' and/or 3' non-coding region, such that the chimera has improved characteristics.

Examples of a chimera encoding at least one substitution that improves chimeric virus characteristic are those encoding a polypeptide having one or more amino acid substitution in a DENV E protein. In particular embodiments, the substitution includes, but is not limited to, at least one substitution at DENV E protein amino acid position 64, 122, 186, or 203 of the DEN2 E protein, or a combination of two or more thereof. It is to be understood that substitutions at the equivalent E protein amino acid positions in DEN1, DEN3, or DEN4 are also contemplated. Furthermore, substitutions at the equivalent position are contemplated even in situations where the wild type amino acid is different from the amino acid in the wild type DEN2 (for example, DEN2 E protein includes

Lys at position 64, while the equivalent amino acid in DEN4 E protein is Ser64). In some examples, the amino acid substitution alters a positively charged residue (such as Lys, Arg, or His; for example, Lys64 or Lys 122) to a non-charged residue (for example, Met, Ser, Thr, Gly, Ala, Val, Leu, Ile, or Val) or to a negatively charged residue (for example, Asp or Glu). The particular substitution (expressed as in DEN2) may include K64M, K64S, K64T, K122L, K122I, K122T, and/or K122E. In other examples, the amino acid substitution alters a polar residue (such as Ser or Thr; for example, Ser186 of DEN2) to a negatively charged residue (for example, Asp or Glu) or a hydrophobic residue (such as phenylalanine). In further examples, the amino acid substitution includes a substitution at amino acid position 203 of the E protein (expressed as in DEN2), for example N203D. In particular examples, the disclosed chimeric flavivirus encodes a DEN2 E protein including K122I, S186F, N203D, or a combination of two or more thereof.

In some embodiments, the disclosed chimeric flavivirus encodes at least one amino acid substitution in the DENV prM protein that improves virus characteristics. In one example, the substitution includes a substitution at amino acid position 149 of the DEN2 prM protein. It is to be understood that substitutions at the equivalent prM protein amino acid positions in DEN1, DEN3, or DEN4 are also contemplated. Furthermore, substitutions at the equivalent position are contemplated even in situations where the wild type amino acid is different from the amino acid in the wild type DEN2 (for example, DEN2 prM protein includes Phe at position 149, while the equivalent amino acid is Thr in DEN1 and DEN3 and is Ile in DEN4). In a particular example, the amino acid substitution alters Phe149 of DEN2 prM to an non-charged amino acid (for example, Met, Thr, Gly, or Ile), such as an amino acid residue that is found at the equivalent position in the Japanese encephalitis complex (for example, WNV, Japanese encephalitis virus, St. Louis encephalitis virus, or Murray Valley encephalitis virus).

In additional embodiments, the disclosed chimeric flavivirus may encode at least one amino acid substitution in each of the DENV prM and E proteins. In other examples, the chimeric flavivirus may encode two or more amino acid substitutions in the DEN prM protein or the E protein. For example, the chimeric flavivirus may include at least one amino acid substitution in the DEN E protein (such as Lys64, Lys122, Ser186, and/or Asn203) and at least one amino acid substitution in the DEN prM protein (such as Phe149).

In further examples, the disclosed chimeric flavivirus encodes at least one amino acid substitution, insertion, or deletion in at least one non-structural protein (for example, NS1, NS2A, NS2B, NS3, NS4A, NS4B, or NS5) or C protein of the WNV that improves virus characteristics. For example, the chimeric flavivirus may encode one or more amino acid substitutions in non-structural protein NS2A that may increase virus titer, replication rate, or plaque size, or may stabilize growth of the disclosed chimeras in cell culture. In some examples, the amino acid substitution may include substitutions at one or more of Val23 of NS2A (such as V23M or V23C), 11e49 of NS2A (such as I49T), and Phe94 (such as F94L). Other variant chimeras may encode one or more substitutions in non-structural protein NS1, NS3, and/or NS4A. These variants may alter virus characteristics, for example increasing temperature sensitivity or decreasing infectivity in mosquitoes. In particular examples, the substitution may include Gly53 of NS1 (for example G53D). In other examples the substitution may include amino acid positions 249 and/or 251 of NS3 (such as P249T, P249H, E251V, or E251Q). In still further examples, the flavivirus chimera may encode one

or more substitution in non-structural protein NS4B (such as Thr241 of NS4B, for example T241I).

In some embodiments, the disclosed chimeras may include at least one nucleotide substitution, insertion, or deletion in the 5' and/or 3' non-coding region of the WNV backbone, such that the substitution, insertion, or deletion improves virus characteristics such as replication rate, virus titer, plaque size, stability in cell culture, or infectivity in mammals or mosquitoes. In one example, the chimera includes insertion of a microRNA (miRNA, such as miR-14 (Mead and Tu, *BMC Genomics* 9:244, 2008)) in the 5' or 3' non-coding region to decrease virus replication in mosquitoes. In other examples, the nucleic acid substitution, insertion, and/or deletion may decrease virus replication in mosquitoes or mice.

In additional examples, the chimeras include a combination of two or more nucleic acid substitutions in the non-coding regions, in the nucleic acid sequences encoding the C, prM, E, or non-structural proteins, or any combination thereof. For example, the chimera may include one, two, three, or more substitutions in the DEN prM or E proteins. The chimera may also include one, two, three, or more substitutions in the WNV C protein, non-structural proteins, or non-coding regions. In particular examples, the chimeric flavivirus encodes a DEN2 E protein including N203D and an NS2A protein including I49T and F94L. In other examples, the chimeric flavivirus encodes a DEN2 E protein including K122L, S186F, and N203D, a WNV NS2A protein including I49T and F94L, and a WNV NS4B protein including T241I.

The disclosure also provides WN/DEN chimeras encoding at least one amino acid substitution in the E protein, wherein antibody cross-reactivity of the E protein is measurably reduced. In some examples, the chimera encodes at least one amino acid substitution, for example at DEN2 E protein amino acid position 101, 106, 107, 108, 135, or a combination of two or more thereof. It is to be understood that substitutions at the equivalent E protein amino acid positions in DEN1, DEN3, or DEN4 are also contemplated. Furthermore, substitutions at the equivalent position are contemplated even in situations where the wild type amino acid is different from the amino acid in the wild type DEN2. Particular amino acid substitutions include, but are not limited to, W101F, G106A, G106L, L107F, F108W, F108M, F108V, F108L, L135W, or L135K. Additional examples of amino acid substitutions which reduce antibody cross-reactivity of flavivirus E proteins are known in the art (see e.g. WO06/025990; incorporated herein by reference). Chimeras that include mutations that reduce E protein antibody cross-reactivity may also include one or more additional mutations in the structural proteins, non-structural proteins, or NCRs, such as those described above.

Methods to assess the characteristics of the above-described WN/DEN chimeric viruses including sequence variants are well-known in the art. For example, methods of assessing viral titer, replication rate, plaque size, and stability in culture may be assessed as described in Example 2. See also, Obijeski et al., *J. Gen. Virol.* 22:21-33, 1974; Beaty et al., *Diagnostic Procedures for Viral, Rickettsial, and Chlamydial Infections*, pp. 189-212, Lennette et al. (eds.), 7th Edition, American Public Health Association, 1995; *Virology Methods Manual*, Mahy and Kangro (eds.), Academic Press, 1996; Huang et al., *J. Virol.* 77:11436-11447, 2003; Huang et al., *J. Virol.* 79:7300-7310, 2005. Methods to assess infectivity in mammals (such as mice) or mosquitoes can be carried out as described below (such as Examples 4, 6, and 7).

Reduction in antibody cross-reactivity can be determined by comparing antibody binding affinity of an antibody for the

wild type E protein with antibody binding affinity for an E protein including one or more amino acid substitutions. A reduction in antibody binding affinity indicates a reduction in antibody cross-reactivity. Antibody binding affinities can be determined by many methods well known in the art, such as end-point titration in an Ag-ELISA assay, competition binding in an ELISA assay, a solid-phase radioimmunoassay, and the Biacore® surface plasmon resonance technique (Malmqvist, *Biochem. Soc. Trans.* 27:335-40, 1999; and Drake et al., *Anal. Biochem.* 328:35-43, 2004). In some embodiments the antibody is a polyclonal antibody or a mAb. A specific, non-limiting example of a polyclonal antibody is polyclonal anti-DEN2 murine hyperimmune ascitic fluid. Specific, non-limiting examples of mAbs include 4G2 (ATCC No. HB-112), 6B6C-1, 1B7-5, 1A1D-2, 1A5D-1, 1B4C-2, F4540, D1-11, 9F10, D2811, 2H3, 9A3D-8, 3H5, 1F1, 8A1, or 1H10 (see, e.g., Roehrig et al., *Virology* 246:317-28, 1998; Crill and Chang, *J. Virol.* 78:13975-13986, 2004). Antibody cross-reactivity may be assessed as described in Example 10.

V. Preparation of Viruses and Virus Particles

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, Rickettsial, and Chlamydial Infections*, pp. 189-212, Lennette et al. (eds.), 7th Edition, American

Public Health Association, 1995; *Virology Methods Manual*, Mahy and Kangro (eds.), Academic Press, 1996.

The chimeric viruses of the present invention 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). 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, virus is harvested from the medium in which the cells have been cultured, and harvested virus is treated with a nuclease (e.g., an endonuclease that degrades both DNA and RNA, such as Benzonase; U.S. Pat. No. 5,173, 418). The nuclease-treated virus is then concentrated (e.g., by use of ultrafiltration using a filter having a molecular weight cut-off of, e.g., 500 kDa (e.g., a 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. Virus particles may be purified as discussed herein (see, e.g., section VIII), for example, by ultracentrifugation through a sucrose gradient and sucrose cushion.

VI. Detection of Flavivirus Antibodies

The present disclosure further provides a method of detecting a flavivirus-reactive antibody in a sample (such as a sample from a subject, for example, a blood sample), including contacting the sample with a chimeric virus of this disclosure under conditions whereby an antibody/polypeptide complex can form; and detecting formation of the complex, thereby detecting flavivirus antibody in a sample. An advantage of the disclosed WN/DEN chimeras is that they grow faster and to higher titers and produce larger plaques than wild type DENV. Therefore, the disclosure provides methods of detecting DENV-reactive antibody in a sample that are faster and more specific than methods utilizing wild type DENV. For example, the specificity of the assay (for example

to distinguish between DENV serotypes) may be improved by use of the disclosed chimeras which include amino acid substitutions in the E protein which reduce antibody cross-reactivity.

The method of detecting flavivirus-reactive antibody in a sample can be 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 can include 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 Dengue virus antibody can be detected in a sample from a subject utilizing a disclosed chimeric flavivirus in a plaque-reduction neutralization test (PRNT) assay (see e.g., Example 9). In the PRNT assay, a sample is contacted with a virus encoded by a chimeric flavivirus disclosed herein (such as a WN/DEN2 virus). A suitable cell culture (such as Vero, C6/36, 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 formation and the number of plaques formed in a culture inoculated with the chimeric virus-sample mixture is compared to the number of plaques formed in a control culture (such as cells inoculated with virus alone). A reduction in the number of plaques 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 DENV neutralizing antibody in the sample.

Enzyme immunoassays such as IFA, ELISA and immunoblotting can be readily adapted to accomplish the detection of flavivirus antibodies in a sample according to the methods of this disclosure. An ELISA method effective for the detection of the antibodies can, for example, be as follows: 1) bind the chimeric virus or virus particles to a substrate; 2) contact the bound chimeric virus with a fluid or tissue sample containing the antibody; 3) contact the above with a secondary antibody bound to a detectable moiety which is reactive with the bound antibody (for example, horseradish peroxidase enzyme or alkaline phosphatase enzyme); 4) contact the above with the substrate for the enzyme; 5) contact the above with a color reagent; and 6) observe/measure color change or development.

The 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 this invention 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, IFA according to standard methods.

As a further example, a micro-agglutination test can be used to detect the presence of flavivirus 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. Briefly, microsphere beads are coated with a chimeric flavivirus or virus particle of this disclosure and mixed with a sample, such that antibodies in the sample that are specifically reactive with an antigen encoded by the virus bind the antigen. The bead-bound virus-antibody complexes are allowed to react with fluorescent-dye labeled anti-species antibody (such as FITC-labeled goat anti-human IgM), and are measured using a microsphere reader (such as a Luminex instrument).

VII. Evaluation of Candidate Vaccine Efficacy

The chimeric flaviviruses disclosed herein may be used in methods to assess the efficacy of candidate vaccines, such as DENV vaccine candidates. A number of candidate DENV vaccines have been developed previously, such as attenuated vaccine strains (for example DEN2 PDK-53, DENT PDK-13, DEN3 PGMK-30/FRhL-3, and DEN4 PDK-48) and chimeric DENV constructs (see e.g. U.S. Pat. No. 7,094,411). However, currently there is no ideal mouse model for evaluation of candidate DENV vaccines, because outbred immune competent mice do not succumb to wild type DENV challenge and do not generate sufficient viremia for measuring a protective effect of a candidate vaccine.

The efficacy of candidate DENV vaccines may be 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 DENV strain. The disclosed WN/DENV chimeras may be 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 DENV vaccine (for example, DENV2 PDK-53 strain). Administration of the candidate vaccine strain virus may be carried out by any suitable means, including both parenteral injection (such as intraperitoneal, subcutaneous, or intramuscular injection), by in ovo injection in birds, orally, and by topical application of the virus (typically carried in the pharmaceutical formulation) to an airway surface. Topical application of the virus to an airway surface can be carried out by intranasal administration (e.g. by use of dropper, swab, or inhaler which deposits a pharmaceutical formulation intranasally) or by inhalation administration, such as by creating respirable particles of a pharmaceutical formulation (including both solid particles and liquid particles) containing the virus as an aerosol suspension, and then causing the subject to inhale the respirable

particles. In a particular example, the subjects are inoculated intraperitoneally with 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 are challenged with a virulent or lethal dose (such as a lethal dose determined as in Example 8) of a flavivirus chimera disclosed herein (for example a WN/DEN chimera, such as that encoded by one of SEQ ID NOs: 1, 3, 5, or 7) 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 may be 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.

VIII. Production of Purified Virus Particles Containing Dengue prM and E Proteins

The chimeras disclosed herein may also be used to rapidly produce quantities of virus particles containing DENV prM (or M) and E proteins, as wild type and attenuated DENV strains generally do not replicate efficiently in culture.

Methods of protein purification are well-known in the art (see e.g. Scopes, *Protein Purification: Principles and Practice*, 3rd edition, Springer, 1994). Examples of methods of protein purification include immunoaffinity purification, ultracentrifugation over a gradient, ion exchange chromatography, and gel filtration.

In one example, a method is disclosed of producing virus particles containing Dengue virus E and prM (or M) proteins. The method includes producing the chimeric flaviviruses disclosed herein in a cell culture system, such as Vero, C6/36, LLC-MK₂, or BHK cells. The cells are infected with a WN/DEN chimera and incubated for sufficient time for virus to be produced (for example, at least 2 days, 3 days, 4 days, 5 days, 8 days, or 10 days). A supernatant, such as the cell culture medium, containing the chimeric virus is collected and condensed by PEG-precipitation. The virus particles are then purified through ultracentrifugation over a gradient (such as sucrose or glycerol/potassium tartrate gradient). See e.g., Obijeski et al., *J. Gen. Virol.* 22:21-33, 1974. In a particular example, Vero or C6/36 cells are infected with the disclosed WN/DEN2 chimera and the viral particle with DEN2 prM and/or E protein is purified.

Purified virus particles containing DENV prM and E proteins are suitable for use in place of proteins prepared by other means (such as recombinant expression in mammalian cells, yeast, or *E. coli*). For example, purified virus particles of the disclosed chimeric viruses with DENV prM and/or E proteins may be used in methods of detecting antibodies against these proteins (such as diagnostic tests or assays to determine response to a candidate vaccine). For example, purified virus particles may be immobilized on a solid support and utilized in immunodetection methods such as ELISA, competitive

inhibition assays, micro-agglutination test, or microsphere based immunoassays. Further, the purified virus particles are suitable for use in PRNT assays for detection of neutralizing DENV antibodies.

Further, because the disclosed WN/DEN chimeric viruses grow more rapidly in culture and to higher titers than DEN viruses, purified virus particles containing DENV prM and/or E proteins are useful for production of DENV antigens. Uses for these antigens include production and testing of vaccine candidates and use of virus particles for further study of protein folding, three-dimensional structure, and epitope mapping.

IX. Mosquito Infectivity and Transmissibility

Aedes aegypti mosquito is the major vector for DENV, while *Culex quinquefasciatus* and *Culex pipiens* mosquitoes are the natural vectors for WNV. The disclosed chimeric flaviviruses may have reduced or eliminated infectivity and/or transmissibility in one or more mosquito vectors. Methods for determining whether a virus can infect or be transmitted by a mosquito species or strain are known to one of skill in the art.

By way of example, to determine if the disclosed chimeric viruses can infect *A. aegypti*, *C. quinquefasciatus*, *C. pipiens*, or other mosquito species, mosquitoes can be fed bloodmeal containing virus (such as a 1:1 mixture of cell supernatant from infected cells and defibrinated calf or sheep blood) or by intrathoracic inoculation with medium containing virus (such as about 10⁵ to 10⁷ pfu).

Infected or control mosquitoes are cold anesthetized and dissected. Midguts and/or heads are collected and fixed in either acetone (heads) or 4% paraformaldehyde (midguts) and stained by immunofluorescence assay with a pan-flavivirus E protein antibody, such as 4G2, or serotype-specific antibodies, such as 3H5 (DEN2), 1F1 (DENT), 8A3 (DEN3), or 1H10 (DEN4). A fluorescein-conjugated antibody (such as goat anti-mouse IgG antibody) is used for secondary detection. Tissue immunofluorescence assays are read using a fluorescent microscope.

Decreased E protein immunofluorescence in mosquitoes infected with chimeric WN/DEN virus as compared to control samples (those infected with DENV or WNV) indicates that the chimeric virus has decreased infectivity and/or transmissibility in a particular mosquito species as compared to the wild type DENV or WNV. An increase in E protein immunofluorescence in mosquitoes infected with chimeric WN/DEN virus as compared to control samples (such as those infected with DENV or WNV) may indicate that the chimeric virus has increased infectivity and/or transmissibility in a particular mosquito species as compared to the wild type DENV or WNV.

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

EXAMPLES

Example 1

Construction of WN/DEN2 Chimeric Virus

This example describes construction of a chimeric West Nile/Dengue-2 virus consisting of the prM and E genes from DEN2 in a WNV backbone.

A WNV NY99 infectious clone (designated as WN/IC-P991 clone) in a two plasmid system was used. pWN-AB-Asc contained nucleotides 1 to 2495 and pWN-CG contained

nucleotides 2495-11029 (described in Kinney et al., *J. Gen. Virol.* 87:3611-3622, 2006). Site-directed mutagenesis of pWN-AB-Asc was performed using the QuikChange® Multi site-directed mutagenesis kit (Stratagene, La Jolla, Calif.) to create a SacII site at nucleotides 412-418 and a BspEI site at nucleotides 2424-2429 of the WNV genome. Using similar site-directed mutagenesis, these sites were engineered in a DEN2 16681 infectious clone (D2/IC-30P-A; Kinney et al., *Virology* 230:300-308, 1997) to generate D2IC-30P-NBX clone. Restriction digestion with SacII and BspEI was used to cut the prM and E genes (bp 398-2430) out of both the DEN2 16681 and WNV infectious clones. The prM (including the DEN2 prM signal sequence at the end of the C gene, which serves as an anchor for the C protein during polyprotein processing) and E genes of DEN2 16681 was ligated in the pWN-AB-Asc plasmid, replacing the WNV prM and E genes with the DENV equivalents, to create pWN/D2-AB.

Full length genomic cDNA was prepared by cleaving pWN/D2-AB and pWN-CG at the natural NgoMIV site located at by 2495 of the WNV genome. The two plasmids were then ligated together at the NgoMIV site and transcribed using the AmpliScribe™ T7 kit (Epicentre Technologies, Madison, Wis.). FIG. 1 shows a schematic diagram of the WN/DEN2 chimera (WN/D2) and the junction between the WN C protein and the DEN2 prM signal sequence and prM protein.

In vitro transcription was carried out at 37° C. for 2-3 hours and C6/36 or Vero cells were transfected with the transcribed RNA by electroporation. Infectious virus was collected 4-7 days post transfection. Virus was designated as C6/36-0 seed when recovered from transfected C6/36 cells, and as Vero-0 when recovered from transfected Vero cells. The C6/36-0 and Vero-0 seeds were used to infect C6/36 and Vero cells, respectively, to obtain the C6-1 and V-1 working seeds. To verify the genome accuracy of the recovered chimeras, viral RNA was extracted from C6-1 virus using the QIAamp® Kit (Qiagen Inc, Valencia, Calif.) and cDNA products were generated using the Titan™ One-Tube RT-PCR system (Roche Applied Science, Indianapolis, Ind.). PCR products were directly sequenced to confirm the genome sequence of the chimeric WN/DEN2 virus (SEQ ID NO: 1).

Example 2

WN/DEN2 Chimeric Virus Replication and Titration in Cells

This example describes the replication of a WN/DEN2 chimeric virus in C6/36 and Vero cell lines.

Methods

Three T75 flasks of C6/36 and Vero cells were infected at a multiplicity of infection (MOI) of 0.001 with each of the following viruses: WN NY99, DEN2 681, or WN/DEN2 virus (produced as described in Example 1). Viruses in either 3 ml of Ye-Lah medium (10 g yeast extract and 50 g lactalbumin hydrolysate per 1000 ml water) containing 2% fetal calf serum (C6/36 cells) or 3 ml of Iscove's Modified DMEM (e.g. Gibco-Invitrogen, Carlsbad, Calif.) containing 2% fetal calf serum (Vero cells) were added to the monolayer when the cells were 95-100% confluent. Following infection, flasks were incubated at 28° C. and 37° C. for C6/36 and Vero cells, respectively. Flasks were rocked every 15 minutes for 1.5 hours for viral adsorption. After 1.5 hours, 27 ml of growth medium was added to each flask and the flasks were incubated at 28° C. for C6/36 cells or 37° C. for Vero cells for 10 days. Every 2 days an aliquot of 300 µL was removed from each flask and combined with 300 µL of Iscove's DMEM contain-

ing 35% fetal calf serum. All aliquots were stored at -80° C. until they could be titrated by plaque assay on Vero cells. After plaque titration of each aliquot, the viral growth kinetics in each cell type was established, and also used to determine the proper seed harvest day when producing chimera seeds. When producing chimeric virus seeds, the culture conditions were proportionally scaled up to larger tissue culture vessels.

Virus samples were titrated by plaque assay on Vero cells. Serial 10-fold dilutions of all virus samples were made in BA-1 diluent. 100 µL of each dilution was added to one well of a 6-well tissue culture plate containing a confluent monolayer of Vero cells. Following inoculation, plates were incubated at 37° C. in an atmosphere of 5% CO₂ for 1.5 hours to allow virus adsorption. Plates were rocked every 10 minutes to ensure that the monolayer did not dry out. After virus adsorption all wells were overlaid with 4 ml of 0.8% agarose overlay containing a balanced salt solution and Ye-Lah medium. Plates were incubated at 37° C. in an atmosphere of 5% CO₂ for the indicated times. Following incubation, wells were overlaid with another 2 ml of agarose overlay that also contains 1.5% neutral red to visualize plaques. Plates were read and plaques were counted the following day.

Plaque isolation and serial passage of the chimera in Vero cells was performed. One of the large plaques from the V-1 seed (as V-2) was isolated from the titration plate, and used to infect a flask of fresh Vero cells. The culture medium harvested from this flask was designated as V-3 seed, and was serially passaged through Vero cells seven more times to obtain the V-4 to V-10 seeds. Additionally, the plaques produced from the C6-1 working seed in the Vero plaque titration plate also showed a small portion of larger plaques among the pin-point size plaques. One large plaque was isolated from the plate (as C6-1V-1) and used to infect a flask of fresh Vero cells to obtain C6-1V-2 seed.

PRNT tests were performed by incubating viruses with serial dilutions of a WNV hyperimmune mouse ascitic fluid (HMAF; M28548), a WNV E protein-specific monoclonal antibody (MAb3.67G), a DEN2 HMAF (VS0090), or a DENV-2 E protein-specific monoclonal antibody (MAb3H5) at 4° C. overnight. The following day, samples were added to Vero cells in 6-well culture plates and followed by overlay procedure as in the plaque titration method described above. Neutralization titer was determined as the greatest antibody dilution that decreased plaques by at least 50% compared to the back titration results of the input virus in the same assay.

Results

The WN/DEN2 chimeric virus replicated efficiently and reached high titers in C6/36 cells (8.6 log₁₀ pfu/ml for C6-1 seed). Plaque formation was also assessed in Vero cells. Titers of the working seed after one passage in Vero cells (V-1 seed) was about 4-5 log₁₀ pfu/ml. Compared to the plaque size of the parental D2 16681 and WN NY 99 viruses in Vero cells, the chimeric WN/DEN2 virus formed plaques that were much larger than the D2 16681 virus on day 8 post-infection (p.i.) (FIG. 2), but still smaller than the fast growing WN NY99 virus, which would lyse the whole cell sheet on day 8 post infection.

Plaques were visualized and measured on day 5 p.i. after passage in C6 or Vero cells (FIG. 3). Wild type West Nile NY99 virus (WNV NY99) and DEN-2 16681 virus were included in the same experiment for comparison. WNV NY99 produced large plaques at day 5 p.i., while no plaques were visible for DEN-2 16681 at this time point. Plaque size increased following additional passages in Vero cells (Table 3).

Full genome sequence was obtained for the C6-1 working seed as well as the serial Vero passage seeds, V-3, V-10, and

C6-1V2. The consensus sequence of the C6-1 seed showed no mutation compared to the parent West Nile and DEN-2 viruses from which it was derived. The C6-1V-2 seed contained two silent mutations (nucleotide 3291 of SEQ ID NO: 1 C>T and 8469 of SEQ ID NO: 1 A>G) and one missense mutation (nucleotide 1558 of SEQ ID NO: 1; A>G), resulting in an amino acid change from N to D at position 203 of the DEN2 E protein (amino acid 488 of SEQ ID NO: 2; E-N203D). The V-3 passage had two silent mutations (nucleotide 1566 of SEQ ID NO: 1 T>C and nucleotide 2973 of SEQ ID NO: 1 T>C) and three missense mutations, nucleotide 1558 of SEQ ID NO: 1 (A>G), nucleotide 3638 of SEQ ID NO: 1 (T>C), and nucleotide 3772 of SEQ ID NO: 1 (T>C). These missense mutations resulted in amino acid substitutions in the DEN2 E protein E-N203D (amino acid 488 of SEQ ID NO: 2) and the WNV NS2A protein, NS2A-I49T (amino acid 1181 of SEQ ID NO: 2) and NS2A-F94L (amino acid 1226 of SEQ ID NO: 2). The V-10 seed showed 4 silent mutations (nucleotide 1566 of SEQ ID NO: 1 T>C, nucleotide 2973 of SEQ ID NO: 1 T>C, nucleotide 3600 of SEQ ID NO: 1 T>T/C mix, and nucleotide 6181 of SEQ ID NO: 1 C>C/T mix) and 6 missense mutations (nucleotides 1316 A>T/A, 1508 C>T, 1558 A>G 3638 T>C, 3772 T>C, and 7604 C>T, all numbered as in SEQ ID NO: 1). The resulting amino acid changes are shown in Table 3. Two of the missense mutation loci had mixed nucleotides, resulting in a mixed genotype of E-K122I/K (amino acid 407 of SEQ ID NO: 2) and NS4B-T241T/I (amino acid 2503 of SEQ ID NO: 2).

The E-N203D mutation was found in two seeds (C6-1/V-2 and V-3) that were descendents from separate virus seeds derived from independent experiments. This indicates that this particular mutation may be critical for the chimera adapting to the Vero cell cultures. This mutation may also slightly increase the plaque size of the chimera in Vero cells, further supporting its effect on virus growth in Vero. In addition, the two NS2A mutations in the V-3 seed, NS2A-I49T and NS2A-F94L, also significantly increased the virus growth in Vero cells, resulting in larger plaques compared to the C6-1/V-2 seed. The E-K122I mutation (which eliminates the positive charge at E protein amino acid 122) may also be a Vero cell-adapting mutation for DEN2.

TABLE 3

Plaque size and sequence of successive passages of WN/DEN2				
Virus	Passage History	Amino Acid Mutations		Plaque Size at Day 5 p.i. (mm)*
		Protein	Mutation	
WNV NY99	LLC-MK2-1	N/A	N/A	5.18 +/- 0.37
DENV-2 16681	C6-1	N/A	N/A	Could not be visualized
WN/D2	C6-1	None	None	0.48 +/- 0.08
WN/D2	C6-1/V-2	E	N203D	1.05 +/- 0.16
WN/D2	V-3	E	N203D	1.55 +/- 0.20
		NS2A	I49T	
		NS2A	F94L	
WN/D2	V-10	E	K122I/K	1.78 +/- 0.43
		E	S186F	
		E	N203D	
		NS2A	I49T	
		NS2A	F94L	
		NS4B	T241T/I	

*mean ± standard deviation

N/A: not applicable

The growth kinetics of the wild type and chimeric viruses were tested in both Vero and C6/36 cells. Vero cells were infected with chimeric WN/DEN2, WNV NY99, or DENV-2 16681 at the same multiplicity of infection (MOI) and titer

was determined for 10 days (FIG. 4). Wild type WNV NY99 reached its maximum titer (8.8 log₁₀ pfu/ml) by day 2 and the titer dropped rapidly in subsequent days. WN/DEN2 V-10 seed also reached its maximum titer by day 2 (6.3 log₁₀ pfu/ml), but only decreased slightly in titer by day 10. WN/DEN2 V-3 and C6-1/V-2 seeds approached their maximum titers (5.5 log₁₀ pfu/ml and 5.6 log₁₀ pfu/ml, respectively) by day 4 and then remained fairly consistent (with a slight overall increase) through day 10. WN/DEN2 C6-1 grew more slowly, reaching its maximum titer at day 6 (84.8 log₁₀ pfu/ml). DENV-2 16681 also reached its maximum titer (5.5 log₁₀ pfu/ml) at day 6 and remained fairly consistent throughout the remaining days.

Virus replication in C6/36 cells showed that chimeric WN/DEN2 viruses all reached peak titers of approximately 8.5 log₁₀ pfu/ml (FIG. 5), similar to that of DENV-2 16681. WNV NY99 reached a peak titer of 9.6 log₁₀ pfu/ml. Except for the V-10 seed, all the chimeric viruses reached peak titers at day 6 p.i., similar to WNV NY99. The V-10 seed reached peak titer on day 8, and had a very similar growth profile to that of DENV-2 16681.

Plaque reduction neutralization (PRNT) tests were performed on WNV NY99, DENV-2 16681, WN/DEN2 C6-1, WN/DEN2 C6-1/V-2, WN/DEN2 V-3, and WN/DEN2 V-10 to determine their antigenic profile (Table 4). Although, the endpoint of some of the PRNT titers was not determined, all the chimeras had a similar neutralization pattern to the wt DENV-2 16681 by all 4 tested antibodies. The traditional PRNT of the DENV-2 16681 virus usually takes about 8-10 days due to the slow growth and tiny plaques produced by the virus. On the other hand, all the WN/D2 seeds tested showed plaques by day 5 p.i., resulting in faster PRNT. The similar PRNT patterns to those of wt DENV-2 and the rapid plaque forming ability make WN/D2 chimeras suitable as a surrogate DENV-2 virus in diagnosis by PRNT.

TABLE 4

PRNT assay of WN/DEN2 chimeric viruses				
Virus	PRNT ₅₀ Titer*			
	WNV HMAF (M28548)	WNV E-Specific MAb (MAb3.67G)	DENV-2 HMAF (VS0090)	DENV-2 E-Specific MAb (MAb3H5)
WNV NY99	10240	>40960	<160	<80
DENV-2 16681	<640	<1280	5120	>2560
WN/D2 C6-1	<640	<1280	>5120	>2560
WN/D2 C6-1/V-2	<640	<1280	5120	>2560
WN/D2 V-3	<640	<1280	5120	>2560
WN/D2 V-10	<640	<1280	>5120	>2560

*Greatest antibody dilution that decreased plaques by at least 50%.

Example 3

Characteristics of WN/DEN2 Chimeras with Specific Mutations

This example describes the in vitro characteristics of WN/DEN2 chimeras containing specific introduced mutations.

Methods

To further modify the chimeric WN/DEN2 virus for adapting to mammalian cell cultures, chimeric constructs WN/D2-E203 (containing E-N203D; amino acid 488 of SEQ ID NO: 2), WN/D2-2A (containing NS2A-I49T and NS2A-F94L; amino acids 1181 and 1226 of SEQ ID NO: 2, respectively),

27

and WN/D2-E-2A (containing E-N203D, NS2A-I49T and NS2A-F94L) were made. cDNA fragments containing the E-N203D mutation, or NS2A-I49T and NS2A-F94L mutations were RT-PCR amplified from the C6-1/V-2 seed or V-3 seed (described in Example 2), respectively. The fragment with E-N203D was cloned into the 5'-plasmid containing chimeric WN/DEN2 cDNA from nt 1-2445 (pWN/D2-AB) to obtain new mutant plasmid, pWN/D2-AB-E203. The NS2A mutant fragment (including the silent mutation at nucleotide 2973 of SEQ ID NO: 1 T>C) was cloned into the wt 3'-WN plasmid containing WNV cDNA nt 2440-10996 (pWN-CG) to obtain mutant pWN-CG-2A. WN/D2-E203 was constructed by ligating pWN/D2-AB-E203 with wt pWN-CG by NgoMIV junction (nt 2495 of WNV). WN/D2-2A was constructed by ligating wt pWN/D2-AB with pWN-CG-2A by NgoMIV junction. WN/D2-E2A was made by ligating pWN-AB-E203 with wt pWN-CG-2A by NgoMIV junction. Each chimeric virus was recovered from transfected Vero cells and the working seed (V-1) of each virus was made after one passage of the transfection seed to Vero cells.

Results

Full genome sequencing of the V-1 seed confirmed that no additional missense mutations accrued during replication in Vero cells. Only a silent mutation at nt 2973 of SEQ ID No 1: (T>C) was found in both WN/D2-2A and WN/D2-E2A virus; this mutation was introduced during the cloning of pWN-CG-2A plasmid used in the process of deriving these chimeras.

Plaque assays using each chimera showed that all produced larger plaques in Vero cells than the original WN/D2-C6-1 seed (FIG. 6). Plaques produced by these chimeras could be easily visualized by day 4 p.i. There was a mixed plaque phenotype in the WN/D2-2A seed, which may indicate this virus was still evolving in Vero cells. However, both chimeras with the E-N203D mutation appeared to be quite stable in Vero cells.

Example 4

Determination of Mosquito Infectivity of WN/DEN2 Chimera

This example describes the determination of the ability of WN/DEN2 chimera to infect DENV and WNV mosquito vectors.

Methods

Infectious bloodmeals were made using freshly prepared viruses with an approximate titer of 10^7 pfu/ml in a 1:1 ratio with defibrinated sheep blood. *Aedes aegypti*, *Culex pipiens*, or *Culex quinquefasciatus* mosquitoes were allowed to feed on infectious bloodmeals provided in a HEMOTEK membrane feeder. Bloodfed mosquitoes were held at 28° C. for 10 days. Midguts and heads were dissected, fixed on slides, and stained via immunofluorescence using the pan-flaviviral monoclonal antibody 4G2.

Results

Aedes aegypti mosquito is the major vector for DENV, while *Culex quinquefasciatus* and *Culex pipiens* are the natural vectors for WNV. The WN/DEN2 C6-1 chimera (which lacks any Vero cell-adapting mutations) infects the midgut of *Culex quinquefasciatus* and *Aedes aegypti* in a pattern more similar to that of wild type WNV than wild type DEN2 virus (FIG. 7), suggesting the WNV non-structural genes in the chimera virus have significant effects in infection of these mosquitoes. However, the WN/DEN2 C6-1 virus had similar low infection rate as the DENV-2 in the midgut of *Culex*

28

pipiens, suggesting the structural DENV2 genes in the chimera were controlling the infection in *Culex pipiens*.

Example 5

Construction of Additional WN/DEN Chimeric Viruses

This example describes the construction of chimeric viruses containing the WNV backbone and prM and E protein from DEN1, DEN3, or DEN4.

The prM (including the DEN4 prM signal sequence) and E genes of DEN4, was ligated in the pWN-AB-Asc plasmid, replacing the WNV prM and E genes with the DENV equivalents, to create pWN/D4-AB. Two chimeras were constructed, one with wild type WNV components and one including the WNV NS2A mutations I49T and F94L. Full length genomic cDNA was prepared by cleaving pWN/D4-AB and pWN-CG (or WN-CG-2A) at the natural NgoMIV site located at nt 2495 of the WNV genome. The two plasmids were then ligated together at the NgoMIV site and transcribed using the AmpliScribe™ T7 kit (Epicentre Technologies, Madison, Wis.). FIG. 8 shows a schematic diagram of the WN/DEN4 chimera (WN/D4) and the junction between the WN C protein and the DEN4 prM signal sequence and prM protein. The nucleic acid and amino acid sequences of a WN/DEN4 chimera are provided in SEQ ID NOs: 7 and 8, respectively. The WN/DEN4 chimera having the NS2A mutations had amino acid substitutions at amino acids 1181 and 1226 of SEQ ID NO: 8, respectively.

WN/DEN1 and WN/DEN3 chimeras are created as above and the junction between the WN C protein and the DEN prM signal sequence and prM protein is shown in FIG. 8. The nucleic acid and amino acid sequences of a WN/DEN1 chimera are provided in SEQ ID NOs: 3 and 4, respectively. The WN/DEN1 chimera having the NS2A mutations had amino acid substitutions at amino acids 1181 and 1226 of SEQ ID NO: 4, respectively. The nucleic acid and amino acid sequences of a WN/DEN3 chimera are provided in SEQ ID NOs: 5 and 6, respectively. The WN/DEN3 chimera having the NS2A mutations had amino acid substitutions at amino acids 1179 and 1224 of SEQ ID NO: 6, respectively.

Example 6

Assessment of Neurovirulence and Neuroinvasion Kinetics of Chimeric Virus

This example describes methods for assessing the neurovirulence and neuroinvasion kinetics of WN/DEN chimeric viruses (such as produced in Examples 1 or 5) in mice. Neurovirulence

Groups of 10 mice (such as Swiss Webster, NIH Swiss, or ICR mice) are inoculated intracranially with ten-fold dilutions of WNV and WN/DEN chimeric virus from 0.1 pfu to 1000 pfu. One group of 10 mice is inoculated with 1000 pfu of DENV. The virus is diluted in 30 μ L of sterile phosphate buffered saline (PBS) and is administered via intracranial inoculation. Mice are monitored daily for 4 weeks to determine the virulent dose. Mice showing signs of illness (such as rough fur, hunched back, lethargy, unbalanced or irritable movement, dehydration, 10% weight loss, or signs of paralysis) are euthanized. The results are used to calculate the 50% virulent dose (VD_{50}) of the WNV/DENV chimera. A decreased VD_{50} compared to DEN wild type virus indicates higher neurovirulence than the wild type DENV.

Viremia/Neuroinvasion

Groups of 12 mice (such as Swiss Webster, NIH Swiss, or ICR mice) are inoculated with 1000 pfu of WNV, DENV, and WN/DEN chimera. Virus is inoculated intraperitoneally in 100 μ l of PBS. At days 1, 3, 5, and 7 p.i., mice from each group are sacrificed and blood and brain samples are collected from each mouse. Brains are homogenized in DMEM and both blood and brain titers are determined by plaque assay on Vero cells, as described in Example 2. An increased number of pfu as compared to a control sample (such as a DENV or WNV) indicates increased neuroinvasion or virulence. A decreased number of pfu compared to a control sample (such as a DENV or WNV) indicates decreased neuroinvasion or virulence. Chimeras with higher neuroinvasion are further evaluated in 12-week-old mice for developing a surrogate DENV dose for virulence challenge study as described in Example 8.

Example 7

Determination of Antibody Response to WN/DEN Chimeras

This example describes methods for the determination of antibody responses in mice or other animals inoculated with WN/DEN chimeras. Antibodies to DENV prM and E proteins and WNV non-structural proteins, particularly NS 1, are measured. This example also describes a method for assessing the protective efficacy of immune response to WNV non-structural proteins.

Prior to virus inoculation, pre-immune serum blood samples are collected from all mice by nicking the tail vein. Groups of 10 mice (such as Swiss Webster, NIH Swiss, or ICR mice) are inoculated intraperitoneally with 100 μ L of PBS containing serial ten-fold dilutions of WNV or WN/DEN chimeric virus ranging from 0.1 to 1000 pfu. One group of 10 mice is inoculated with 1000 pfu of DENV. Mice are monitored daily for four weeks and mice showing signs of illness will be euthanized. Four weeks after primary virus inoculation, blood is collected from all surviving mice by nicking the tail vein. Only low dose groups of WNV and chimeric WN/DEN inoculated mice, and mice inoculated with 1000 pfu of DENV are expected to survive. Serum samples from the collected blood are heat-inactivated at 56° C. for 30 minutes and antibodies in the serum are determined by ELISA and/or PRNT assays.

Two days after blood collection, all mice are inoculated with a lethal dose of WNV NY99 (1000 pfu). The virus is delivered in 100 μ l of PBS via intraperitoneal inoculation. Mice are monitored daily and moribund mice are euthanized by overexposure to CO₂ gas. Blood is collected from mice surviving more than 21 days after WNV challenge and antibodies in serum are determined by ELISA and/or PRNT. Antibody responses and survival ratios in the groups that are first inoculated with chimeric WN/DEN virus are used to evaluate the protective efficacy of the immune response triggered by WNV non-structural proteins from the chimeric WN/DEN virus. Increased antibody response and/or survival ratio in animals inoculated with WN/DEN chimeric virus and challenged with WNV indicates that an antibody response and protective immunity are the result of WNV C protein or non-structural proteins.

Example 8

Determination of WN/DEN Lethal Dose and Evaluation of DENV Vaccine Efficacy

This example describes methods for using WN/DEN chimeric viruses to evaluate the efficacy of candidate DENV vaccines.

The lethal dose of WN/DEN chimeric virus is determined in mice by inoculating 12 week old mice (such as Swiss Webster, NIH Swiss, or ICR mice; 8 animals per group) with PBS as a control, or 10, 100, 1000, or 10,000 times the VD₅₀ calculated from the neuroinvasion experiment (described in Example 6) or 10⁴, 10⁵, 10⁶, or 10⁷ pfu, whichever is lower. Mice are inoculated intraperitoneally with virus in 100 μ L of PBS. Mice are monitored for signs of clinical illness daily and moribund mice are euthanized by overexposure to CO₂ gas. The VD₅₀ (the dose causing sickness in 50% of the mice inoculated) is calculated and the lethal dose is generally 10-1000 \times VD₅₀. Usually 100 \times VD₅₀ is used. Alternatively, blood can be collected after virus challenge to determine the viremia levels from each group. Chimeric virus doses causing higher viremia compared to a wild type DENV control group (such as 100-fold, 1000-fold, 10000-fold or higher) may be used for vaccine efficacy study.

To assess candidate DENV vaccine efficacy, groups of 4 week old mice (such as Swiss Webster, NIH Swiss, or ICR mice) are inoculated intraperitoneally with wild type DENV, DENV vaccine strain, or PBS. Mice in each group are inoculated intraperitoneally with 10⁵ pfu of virus in 100 μ l of PBS. Identical immunizations are given four to six weeks later. The mice are given WN/DEN chimeric virus at a lethal dose (100 \times VD₅₀) or a dose causing high viremia compared to wild type DENV when they are 12 weeks old. Mice are bled to determine viremia level and monitored daily for signs of morbidity after lethal virus challenge. Mice with the first sign of morbidity, such as rough fur, hunched back, lethargy, unbalanced or irritable movement, dehydration, 10% weight loss, or signs of paralysis are euthanized immediately by overexposure to CO₂ gas.

Blood is also collected prior to secondary immunization, lethal WN/DEN challenge, and from mice surviving 21-28 days after lethal challenge. Antibodies to DEN or WNV proteins in the serum are determined by PRNT. Protective efficacy of the vaccine is evaluated by comparing viremia levels or survival ratios of the vaccinated groups to the non-immunized control group. Increased survival, decreased viremia level, or increased anti-DENV antibody production of mice inoculated with a candidate vaccine as compared to a control group indicates a DENV vaccine candidate suitable for further testing. No increase in survival or no decrease in viremia level compared to a non-immunized control group indicates poor protective efficacy by the DENV vaccine candidate.

Example 9

Neutralizing Antibody Assays

This example describes methods of assessing neutralizing antibody response to DENV infection or WN/DEN virus chimeras using a plaque-reduction neutralization assay (PRNT) or immunostaining-based neutralization assay.

Serum samples are tested for neutralizing antibodies by serum-dilution PRNT. 60-100 pfu of WN/DEN virus chimera or wild type DENV is incubated with serial 2-fold dilutions of heat-inactivated (56° C. for 30 minutes) serum specimens overnight at 4° C. The virus-serum mixtures are inoculated in tissue culture plates containing a confluent monolayer of Vero cells. Following inoculation, plates are incubated at 37° C. in an atmosphere of 5% CO₂ for 1.5 hours to allow virus adsorption. Plates are rocked every 10 minutes to ensure the cell monolayer does not dry out. After virus adsorption, the cells are overlaid with 0.8% agarose containing balanced salt solution and Ye-Lah medium (10 g yeast extract and 50 g lactalbumin hydrolysate per 1000 ml water). Plates are incubated at

31

37° C. in an atmosphere of 5% CO₂ for 1-7 days. Following this incubation, wells are overlaid with another agarose overlay containing 1.5% neutral red to visualize plaques. Plaques are counted the following 1-3 days.

A reduction in the number of plaques in the cell culture inoculated with the virus-serum mixture as compared to the control culture (cells incubated with virus alone) indicates the presence of a DENV neutralizing antibody in the serum. The neutralizing antibody titer is identified as the highest serum dilution that reduces the number of virus plaques in the test by 50% or more.

In addition to PRNT assay, neutralizing antibody can also be measured by an immunostaining-based neutralization assay. The method is identical to the PRNT assay, up to the step of virus-antibody absorption on cell monolayer in a cell culture plate (6-well, 24-well, 48-well, or 96-well plate) at 37° C. CO₂ incubator. Instead of Ye-Lah medium with agarose overlay, liquid culture medium or medium mixed with Avicel overlay is added to the plates following the virus absorption. Medium or the Avicel overlay is removed after desired incubation periods (e.g. 2-5 days), and cells are fixed with acetone. DENV antibodies are added to the cell plates for 1 hour at 37° C. Plates are washed 3 times to remove unbound antibodies, and chemical or fluorescent conjugated secondary antibody is added to the plate and incubated for 30-60 min at 37° C. The immunostained virus foci in the Avicel overlay plates can be visualized and counted. In the case of using liquid medium in the experiment, the viral antigen produced in the infected cells can be measured by plate reader.

Example 10

Antibody Cross-Reactivity of Chimeric Flaviviruses

This example describes methods for determining reduction of antibody cross-reactivity for DENV E proteins including one or more amino acid substitutions.

DENV E protein (wild type or including one or more amino acid substitutions) is expressed either by infection of cells with a WN/DEN virus chimera encoding a DENV E protein,

32

or by recombinant production of the DENV E proteins (for example by expression in mammalian cells, yeast, or *E. coli*). E protein antigen of the WN/DENV chimera or its variants containing different amino acid substitutions expressed in the chimera-infected C6/36 cells is analyzed with a panel of anti-flavivirus mAbs by IFA to determine mAb end point reactivity of the variant E proteins. Briefly, infected cells are fixed by acetone on microscopy optical slides or slide chambers. Serial diluted mAbs are added to different wells of the slide and incubated at 37° C. for 1 hour and unbound mAb is then rinsed away by PBS. Secondary goat- or rabbit-anti-mouse IgG conjugated with FITC is added and incubated at 37° for 30 min to bind the mouse mAb in the wells, and unbound conjugates is rinsed off by PBS. Positive wells are detected by fluorescent microscope.

Alternatively, purified WN/DENV virus particles are captured in native form by a rabbit anti-DEN polyclonal antibody coated on ELISA plates. The E protein and its variants on the virus particles are analyzed by ELISA with a panel of mouse anti-flavivirus mAbs to determine mAb end point reactivity of the variant viral particles, following the protocol of Roehrig et al. (*Virology* 246:317-28, 1998). The panel of the mAb can include 4G2 (ATCC No. HB-112), 6B6C-1, 1B7-5, 1A1D-2, 1A5D-1, 1B4C-2, F4540, D1-11, 9F-10, D2811, 2H3, 9A3D-8, 3H5, 1F1, 8A1, and/or 1H10.

WN/DEN chimeras including E protein variants that have reduced antibody cross-reactivity may be used for diagnosis of secondary flavivirus infection with a particular DENV serotype (i.e. DEN1, DEN2, DEN3, or DEN4), such as in a PRNT assay. These chimeras may also be included in a flavivirus diagnosis panel, which can reduce false positive results and enhance the speed and accuracy of flavivirus diagnostics.

In view of the many possible embodiments to which the principles of the disclosure may be applied, it should be recognized that the illustrated embodiments are only examples 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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280 285 290	
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Asp Phe Val Glu Gly Val Ser Gly Gly Ser Trp Val Asp Ile Val Leu	
295 300 305 310	
gaa cat gga agc tgt gtg acg acg atg gca aaa aac aaa cca aca ttg	1074
Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr Leu	
315 320 325	
gat ttt gaa ctg ata aaa aca gaa gcc aaa cag cct gcc acc cta agg	1122
Asp Phe Glu Leu Ile Lys Thr Glu Ala Lys Gln Pro Ala Thr Leu Arg	
330 335 340	

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aag tac tgt ata gag gca aag cta acc aac aca aca aca gaa tct cgc	1170
Lys Tyr Cys Ile Glu Ala Lys Leu Thr Asn Thr Thr Thr Glu Ser Arg	
345 350 355	
tgc cca aca caa ggg gaa ccc agc cta aat gaa gag cag gac aaa agg	1218
Cys Pro Thr Gln Gly Glu Pro Ser Leu Asn Glu Glu Gln Asp Lys Arg	
360 365 370	
ttc gtc tgc aaa cac tcc atg gta gac aga gga tgg gga aat gga tgt	1266
Phe Val Cys Lys His Ser Met Val Asp Arg Gly Trp Gly Asn Gly Cys	
375 380 385 390	
gga cta ttt gga aag gga ggc att gtg acc tgt gct atg ttc aga tgc	1314
Gly Leu Phe Gly Lys Gly Gly Ile Val Thr Cys Ala Met Phe Arg Cys	
395 400 405	
aaa aag aac atg gaa gga aaa gtt gtg caa cca gaa aac ttg gaa tac	1362
Lys Lys Asn Met Glu Gly Lys Val Val Gln Pro Glu Asn Leu Glu Tyr	
410 415 420	
acc att gtg ata aca cct cac tca ggg gaa gag cat gca gtc gga aat	1410
Thr Ile Val Ile Thr Pro His Ser Gly Glu Glu His Ala Val Gly Asn	
425 430 435	
gac aca gga aaa cat ggc aag gaa atc aaa ata aca cca cag agt tcc	1458
Asp Thr Gly Lys His Gly Lys Glu Ile Lys Ile Thr Pro Gln Ser Ser	
440 445 450	
atc aca gaa gca gaa ttg aca ggt tat ggc act gtc aca atg gag tgc	1506
Ile Thr Glu Ala Glu Leu Thr Gly Tyr Gly Thr Val Thr Met Glu Cys	
455 460 465 470	
tct cca aga acg ggc ctc gac ttc aat gag atg gtg ttg ttg cag atg	1554
Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Gln Met	
475 480 485	
gaa aat aaa gct tgg ctg gtg cac agg caa tgg ttc cta gac ctg ccg	1602
Glu Asn Lys Ala Trp Leu Val His Arg Gln Trp Phe Leu Asp Leu Pro	
490 495 500	
tta cca tgg ttg ccc gga gcg gac aca caa ggg tca aat tgg ata cag	1650
Leu Pro Trp Leu Pro Gly Ala Asp Thr Gln Gly Ser Asn Trp Ile Gln	
505 510 515	
aaa gag aca ttg gtc act ttc aaa aat ccc cat gcg aag aaa cag gat	1698
Lys Glu Thr Leu Val Thr Phe Lys Asn Pro His Ala Lys Lys Gln Asp	
520 525 530	
gtt gtt gtt tta gga tcc caa gaa ggg gcc atg cac aca gca ctt aca	1746
Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu Thr	
535 540 545 550	
ggg gcc aca gaa atc caa atg tca tca gga aac tta ctc ttc aca gga	1794
Gly Ala Thr Glu Ile Gln Met Ser Ser Gly Asn Leu Leu Phe Thr Gly	
555 560 565	
cat ctc aag tgc agg ctg aga atg gac aag cta cag ctc aaa gga atg	1842
His Leu Lys Cys Arg Leu Arg Met Asp Lys Leu Gln Leu Lys Gly Met	
570 575 580	
tca tac tct atg tgc aca gga aag ttt aaa gtt gtg aag gaa ata gca	1890
Ser Tyr Ser Met Cys Thr Gly Lys Phe Lys Val Val Lys Glu Ile Ala	
585 590 595	
gaa aca caa cat gga aca ata gtt atc aga gtg caa tat gaa ggg gac	1938
Glu Thr Gln His Gly Thr Ile Val Ile Arg Val Gln Tyr Glu Gly Asp	
600 605 610	
ggc tct cca tgc aag atc cct ttt gag ata atg gat ttg gaa aaa aga	1986
Gly Ser Pro Cys Lys Ile Pro Phe Glu Ile Met Asp Leu Glu Lys Arg	
615 620 625 630	
cat gtc tta ggt cgc ctg att aca gtc aac cca att gtg aca gaa aaa	2034
His Val Leu Gly Arg Leu Ile Thr Val Asn Pro Ile Val Thr Glu Lys	
635 640 645	
gat agc cca gtc aac ata gaa gca gaa cct cca ttc gga gac agc tac	2082
Asp Ser Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Asp Ser Tyr	
650 655 660	

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atc atc ata gga gta gag ccg gga caa ctg aag ctc aac tgg ttt aag Ile Ile Ile Gly Val Glu Pro Gly Gln Leu Lys Leu Asn Trp Phe Lys 665 670 675	2130
aaa gga agt tct atc ggc caa atg ttt gag aca aca atg agg ggg gcg Lys Gly Ser Ser Ile Gly Gln Met Phe Glu Thr Thr Met Arg Gly Ala 680 685 690	2178
aag aga atg gcc att tta ggt gac aca gcc tgg gat ttt gga tcc ttg Lys Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser Leu 695 700 705 710	2226
gga gga gtg ttt aca tct ata gga aag gct ctc cac caa gtc ttt gga Gly Gly Val Phe Thr Ser Ile Gly Lys Ala Leu His Gln Val Phe Gly 715 720 725	2274
gca atc tat gga gct gcc ttc agt ggg gtt tca tgg act atg aaa atc Ala Ile Tyr Gly Ala Ala Phe Ser Gly Val Ser Trp Thr Met Lys Ile 730 735 740	2322
ctc ata gga gtc att atc aca tgg ata gga atg aat tca cgc agc acc Leu Ile Gly Val Ile Ile Thr Trp Ile Gly Met Asn Ser Arg Ser Thr 745 750 755	2370
tca ctg tct gtg aca cta gta ttg gtg gga att gtg aca ctg tat ttg Ser Leu Ser Val Thr Leu Val Leu Val Gly Ile Val Thr Leu Tyr Leu 760 765 770	2418
gga gtc atg gtg cag gcc gat tcc gga tgt gcc ata gac atc agc cgg Gly Val Met Val Gln Ala Asp Ser Gly Cys Ala Ile Asp Ile Ser Arg 775 780 785 790	2466
caa gag ctg aga tgt gga agt gga gtg ttc ata cac aat gat gtg gag Gln Glu Leu Arg Cys Gly Ser Gly Val Phe Ile His Asn Asp Val Glu 795 800 805	2514
gct tgg atg gac cgg tac aag tat tac cct gaa acg cca caa ggc cta Ala Trp Met Asp Arg Tyr Lys Tyr Tyr Pro Glu Thr Pro Gln Gly Leu 810 815 820	2562
gcc aag atc att cag aaa gct cat aag gaa gga gtg tgc ggt cta cga Ala Lys Ile Ile Gln Lys Ala His Lys Glu Gly Val Cys Gly Leu Arg 825 830 835	2610
tca gtt tcc aga ctg gag cat caa atg tgg gaa gca gtg aag gac gag Ser Val Ser Arg Leu Glu His Gln Met Trp Glu Ala Val Lys Asp Glu 840 845 850	2658
ctg aac act ctt ttg aag gag aat ggt gtg gac ctt agt gtc gtg gtt Leu Asn Thr Leu Leu Lys Glu Asn Gly Val Asp Leu Ser Val Val Val 855 860 865 870	2706
gag aaa cag gag gga atg tac aag tca gca cct aaa cgc ctc acc gcc Glu Lys Gln Glu Gly Met Tyr Lys Ser Ala Pro Lys Arg Leu Thr Ala 875 880 885	2754
acc acg gaa aaa ttg gaa att ggc tgg aag gcc tgg gga aag agt att Thr Thr Glu Lys Leu Glu Ile Gly Trp Lys Ala Trp Gly Lys Ser Ile 890 895 900	2802
tta ttt gca cca gaa ctc gcc aac aac acc ttt gtg gtt gat ggt ccg Leu Phe Ala Pro Glu Leu Ala Asn Asn Thr Phe Val Val Asp Gly Pro 905 910 915	2850
gag acc aag gaa tgt ccg act cag aat cgc gct tgg aat agc tta gaa Glu Thr Lys Glu Cys Pro Thr Gln Asn Arg Ala Trp Asn Ser Leu Glu 920 925 930	2898
gtg gag gat ttt gga ttt ggt ctc acc agc act cgg atg ttc ctg aag Val Glu Asp Phe Gly Phe Gly Leu Thr Ser Thr Arg Met Phe Leu Lys 935 940 945 950	2946
gtc aga gag agc aac aca act gaa tgt gac tcg aag atc att gga acg Val Arg Glu Ser Asn Thr Thr Glu Cys Asp Ser Lys Ile Ile Gly Thr 955 960 965	2994
gct gtc aag aac aac ttg gcg atc cac agt gac ctg tcc tat tgg att Ala Val Lys Asn Asn Leu Ala Ile His Ser Asp Leu Ser Tyr Trp Ile 970 975 980	3042

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gaa agc agg ctc aat gat acg tgg aag ctt gaa agg gca gtt ctg ggt Glu Ser Arg Leu Asn Asp Thr Trp Lys Leu Glu Arg Ala Val Leu Gly 985 990 995	3090
gaa gtc aaa tca tgt acg tgg cct gag acg cat acc ttg tgg ggc Glu Val Lys Ser Cys Thr Trp Pro Glu Thr His Thr Leu Trp Gly 1000 1005 1010	3135
gat gga atc ctt gag agt gac ttg ata ata cca gtc aca ctg gcg Asp Gly Ile Leu Glu Ser Asp Leu Ile Ile Pro Val Thr Leu Ala 1015 1020 1025	3180
gga cca cga agc aat cac aat cgg aga cct ggg tac aag aca caa Gly Pro Arg Ser Asn His Asn Arg Arg Pro Gly Tyr Lys Thr Gln 1030 1035 1040	3225
aac cag ggc cca tgg gac gaa ggc cgg gta gag att gac ttc gat Asn Gln Gly Pro Trp Asp Glu Gly Arg Val Glu Ile Asp Phe Asp 1045 1050 1055	3270
tac tgc cca gga act acg gtc acc ctg agt gag agc tgc gga cac Tyr Cys Pro Gly Thr Thr Val Thr Leu Ser Glu Ser Cys Gly His 1060 1065 1070	3315
cgt gga cct gcc act cgc acc acc aca gag agc gga aag ttg ata Arg Gly Pro Ala Thr Arg Thr Thr Thr Glu Ser Gly Lys Leu Ile 1075 1080 1085	3360
aca gat tgg tgc tgc agg agc tgc acc tta cca cca ctg cgc tac Thr Asp Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr 1090 1095 1100	3405
caa act gac agc ggc tgt tgg tat ggt atg gag atc aga cca cag Gln Thr Asp Ser Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Gln 1105 1110 1115	3450
aga cat gat gaa aag acc ctc gtg cag tca caa gtg aat gct tat Arg His Asp Glu Lys Thr Leu Val Gln Ser Gln Val Asn Ala Tyr 1120 1125 1130	3495
aat gct gat atg att gac cct ttt cag ttg ggc ctt ctg gtc gtg Asn Ala Asp Met Ile Asp Pro Phe Gln Leu Gly Leu Leu Val Val 1135 1140 1145	3540
ttc ttg gcc acc cag gag gtc ctt cgc aag agg tgg aca gcc aag Phe Leu Ala Thr Gln Glu Val Leu Arg Lys Arg Trp Thr Ala Lys 1150 1155 1160	3585
atc agc atg cca gct ata ctg att gct ctg cta gtc ctg gtg ttt Ile Ser Met Pro Ala Ile Leu Ile Ala Leu Leu Val Leu Val Phe 1165 1170 1175	3630
ggg ggc att act tac act gat gtg tta cgc tat gtc atc ttg gtg Gly Gly Ile Thr Tyr Thr Asp Val Leu Arg Tyr Val Ile Leu Val 1180 1185 1190	3675
ggg gca gct ttc gca gaa tct aat tcg gga gga gac gtg gta cac Gly Ala Ala Phe Ala Glu Ser Asn Ser Gly Gly Asp Val Val His 1195 1200 1205	3720
ttg gcg ctc atg gcg acc ttc aag ata caa cca gtg ttt atg gtg Leu Ala Leu Met Ala Thr Phe Lys Ile Gln Pro Val Phe Met Val 1210 1215 1220	3765
gca tcg ttt ctc aaa gcg aga tgg acc aac cag gag aac att ttg Ala Ser Phe Leu Lys Ala Arg Trp Thr Asn Gln Glu Asn Ile Leu 1225 1230 1235	3810
ttg atg ttg gcg gct gtt ttc ttt caa atg gct tat tac gat gcc Leu Met Leu Ala Ala Val Phe Phe Gln Met Ala Tyr Tyr Asp Ala 1240 1245 1250	3855
cgc caa att ctg ctc tgg gag atc cct gat gtg ttg aat tca ctg Arg Gln Ile Leu Leu Trp Glu Ile Pro Asp Val Leu Asn Ser Leu 1255 1260 1265	3900
gcg gta gct tgg atg ata ctg aga gcc ata aca ttc aca acg aca Ala Val Ala Trp Met Ile Leu Arg Ala Ile Thr Phe Thr Thr Thr 1270 1275 1280	3945

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tca aac	gtg gtt gtt cgc ctg	cta gcc ctg cta aca	ccc ggg ctg	3990
Ser Asn	Val Val Val Pro Leu	Leu Ala Leu Leu Thr	Pro Gly Leu	
1285	1290	1295		
aga tgc	ttg aat ctg gat gtg	tac agg ata ctg ctg	ttg atg gtc	4035
Arg Cys	Leu Asn Leu Asp Val	Tyr Arg Ile Leu Leu	Leu Met Val	
1300	1305	1310		
gga ata	ggc agc ttg atc agg	gag aag agg agt gca	gct gca aaa	4080
Gly Ile	Gly Ser Leu Ile Arg	Glu Lys Arg Ser Ala	Ala Ala Lys	
1315	1320	1325		
aag aaa	gga gca agt ctg cta	tgc ttg gct cta gcc	tca aca gga	4125
Lys Lys	Gly Ala Ser Leu Leu	Cys Leu Ala Leu Ala	Ser Thr Gly	
1330	1335	1340		
ctt ttc	aac ccc atg atc ctt	gct gct gga ctg att	gca tgt gat	4170
Leu Phe	Asn Pro Met Ile Leu	Ala Ala Gly Leu Ile	Ala Cys Asp	
1345	1350	1355		
ccc aac	cgt aaa cgc gga tgg	ccc gca act gaa gtg	atg aca gct	4215
Pro Asn	Arg Lys Arg Gly Trp	Pro Ala Thr Glu Val	Met Thr Ala	
1360	1365	1370		
gtc ggc	cta atg ttt gcc atc	gtc gga ggg ctg gca	gag ctt gac	4260
Val Gly	Leu Met Phe Ala Ile	Val Gly Gly Leu Ala	Glu Leu Asp	
1375	1380	1385		
att gac	tcc atg gcc att cca	atg act atc gcg ggg	ctc atg ttt	4305
Ile Asp	Ser Met Ala Ile Pro	Met Thr Ile Ala Gly	Leu Met Phe	
1390	1395	1400		
gct gct	ttc gtg att tct ggg	aaa tca aca gat atg	tgg att gag	4350
Ala Ala	Phe Val Ile Ser Gly	Lys Ser Thr Asp Met	Trp Ile Glu	
1405	1410	1415		
aga acg	gcg gac att tcc tgg	gaa agt gat gca gaa	att aca ggc	4395
Arg Thr	Ala Asp Ile Ser Trp	Glu Ser Asp Ala Glu	Ile Thr Gly	
1420	1425	1430		
tcg agc	gaa aga gtt gat gtg	cgg ctt gat gat gat	gga aac ttc	4440
Ser Ser	Glu Arg Val Asp Val	Arg Leu Asp Asp Asp	Gly Asn Phe	
1435	1440	1445		
cag ctc	atg aat gat cca gga	gca cct tgg aag ata	tgg atg ctc	4485
Gln Leu	Met Asn Asp Pro Gly	Ala Pro Trp Lys Ile	Trp Met Leu	
1450	1455	1460		
aga atg	gtc tgt ctc gcg att	agt gcg tac acc ccc	tgg gca atc	4530
Arg Met	Val Cys Leu Ala Ile	Ser Ala Tyr Thr Pro	Trp Ala Ile	
1465	1470	1475		
ttg ccc	tca gta gtt gga ttt	tgg ata act ctc caa	tac aca aag	4575
Leu Pro	Ser Val Val Gly Phe	Trp Ile Thr Leu Gln	Tyr Thr Lys	
1480	1485	1490		
aga gga	ggc gtg ttg tgg gac	act ccc tca cca aag	gag tac aaa	4620
Arg Gly	Gly Val Leu Trp Asp	Thr Pro Ser Pro Lys	Glu Tyr Lys	
1495	1500	1505		
aag ggg	gac acg acc acc ggc	gtc tac agg atc atg	act cgt ggg	4665
Lys Gly	Asp Thr Thr Thr Gly	Val Tyr Arg Ile Met	Thr Arg Gly	
1510	1515	1520		
ctg ctc	ggc agt tat caa gca	gga gcg ggc gtg atg	gtt gaa ggt	4710
Leu Leu	Gly Ser Tyr Gln Ala	Gly Ala Gly Val Met	Val Glu Gly	
1525	1530	1535		
gtt ttc	cac acc ctt tgg cat	aca aca aaa gga gcc	gct ttg atg	4755
Val Phe	His Thr Leu Trp His	Thr Thr Lys Gly Ala	Ala Leu Met	
1540	1545	1550		
agc gga	gag ggc cgc ctg gac	cca tac tgg ggc agt	gtc aag gag	4800
Ser Gly	Glu Gly Arg Leu Asp	Pro Tyr Trp Gly Ser	Val Lys Glu	
1555	1560	1565		
gat cga	ctt tgt tac gga gga	ccc tgg aaa ttg cag	cac aag tgg	4845
Asp Arg	Leu Cys Tyr Gly Gly	Pro Trp Lys Leu Gln	His Lys Trp	
1570	1575	1580		

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aac ggg Asn Gly 1585	cag gat gag gtg Gln Asp Glu Val 1590	cag Gln 1590	atg att gtg gtg Met Ile Val Val 1595	gaa cct ggc agg Glu Pro Gly Arg 1595	4890
aac gtt Asn Val 1600	aag aac gtc cag Lys Asn Val Gln 1605	acg Thr 1605	aaa cca ggg gtg Lys Pro Gly Val 1610	ttc aaa aca cct Phe Lys Thr Pro 1610	4935
gaa gga Glu Gly 1615	gaa atc ggg gcc Glu Ile Gly Ala 1620	gtg Val 1620	act ttg gac ttc Thr Leu Asp Phe 1625	ccc act gga aca Pro Thr Gly Thr 1625	4980
tca ggc Ser Gly 1630	tca cca ata gtg Ser Pro Ile Val 1635	gac Asp 1635	aaa aac ggt gat Lys Asn Gly Asp 1640	gtg att ggg ctt Val Ile Gly Leu 1640	5025
tat ggc Tyr Gly 1645	aat gga gtc ata Asn Gly Val Ile 1650	atg Met 1650	ccc aac ggc tca Pro Asn Gly Ser 1655	tac ata agc gcg Tyr Ile Ser Ala 1655	5070
ata gtg Ile Val 1660	cag ggt gaa agg Gln Gly Glu Arg 1665	atg Met 1665	gat gag cca atc Asp Glu Pro Ile 1670	cca gcc gga ttc Pro Ala Gly Phe 1670	5115
gaa cct Glu Pro 1675	gag atg ctg agg Glu Met Leu Arg 1680	aaa Lys 1680	aaa cag atc act Lys Gln Ile Thr 1685	gta ctg gat ctc Val Leu Asp Leu 1685	5160
cat ccc His Pro 1690	ggc gcc ggt aaa Gly Ala Gly Lys 1695	aca Thr 1695	agg agg att ctg Arg Arg Ile Leu 1700	cca cag atc atc Pro Gln Ile Ile 1700	5205
aaa gag Lys Glu 1705	gcc ata aac aga Ala Ile Asn Arg 1710	aga Arg 1710	ctg aga aca gcc Leu Arg Thr Ala 1715	gtg cta gca cca Val Leu Ala Pro 1715	5250
acc agg Thr Arg 1720	gtt gtg gct gct Val Val Ala Ala 1725	gag Glu 1725	atg gct gaa gca Met Ala Glu Ala 1730	ctg aga gga ctg Leu Arg Gly Leu 1730	5295
ccc atc Pro Ile 1735	cgg tac cag aca Arg Tyr Gln Thr 1740	tcc Ser 1740	gca gtg ccc aga Ala Val Pro Arg 1745	gaa cat aat gga Glu His Asn Gly 1745	5340
aat gag Asn Glu 1750	att gtt gat gtc Ile Val Asp Val 1755	atg Met 1755	tgt cat gct acc Cys His Ala Thr 1760	ctc acc cac agg Leu Thr His Arg 1760	5385
ctg atg Leu Met 1765	tct cct cac agg Ser Pro His Arg 1770	gtg Val 1770	ccg aac tac aac Pro Asn Tyr Asn 1775	ctg ttc gtg atg Leu Phe Val Met 1775	5430
gat gag Asp Glu 1780	gct cat ttc acc Ala His Phe Thr 1785	gac Asp 1785	cca gct agc att Pro Ala Ser Ile 1790	gca gca aga ggt Ala Ala Arg Gly 1790	5475
tac att Tyr Ile 1795	tcc aca aag gtc Ser Thr Lys Val 1800	gag Glu 1800	cta ggg gag gcg Leu Gly Glu Ala 1805	gcg gca ata ttc Ala Ala Ile Phe 1805	5520
atg aca Met Thr 1810	gcc acc cca cca Ala Thr Pro Pro 1815	ggc Gly 1815	act tca gat cca Thr Ser Asp Pro 1820	ttc cca gag tcc Phe Pro Glu Ser 1820	5565
aat tca Asn Ser 1825	cca att tcc gac Pro Ile Ser Asp 1830	tta Leu 1830	cag act gag atc Gln Thr Glu Ile 1835	ccg gat cga gct Pro Asp Arg Ala 1835	5610
tgg aac Trp Asn 1840	tct gga tac gaa Ser Gly Tyr Glu 1845	tgg Trp 1845	atc aca gaa tac Ile Thr Glu Tyr 1850	acc ggg aag acg Thr Gly Lys Thr 1850	5655
gtt tgg Val Trp 1855	ttt gtg cct agt Phe Val Pro Ser 1860	gtc Val 1860	aag atg ggg aat Lys Met Gly Asn 1865	gag att gcc ctt Glu Ile Ala Leu 1865	5700
tgc cta Cys Leu 1870	caa cgt gct gga Gln Arg Ala Gly 1875	aag Lys 1875	aaa gta gtc caa Lys Val Val Gln 1880	ttg aac aga aag Leu Asn Arg Lys 1880	5745

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tcg tac Ser Tyr 1885	gag acg gag tac Glu Thr Glu Tyr 1890	cca Pro 1890	aaa tgt aag aac Lys Cys Lys Asn 1895	gat Asp 1895	gat tgg gac Asp Trp Asp 1895	5790
ttt gtt Phe Val 1900	atc aca aca gac Ile Thr Thr Asp 1905	ata Ile 1905	tct gaa atg ggg Ser Glu Met Gly 1910	gct Ala 1910	aac ttc aag Asn Phe Lys 1910	5835
gcg agc Ala Ser 1915	agg gtg att gac Arg Val Ile Asp 1920	agc Ser 1920	cgg aag agt gtg Arg Lys Ser Val 1925	aaa Lys 1925	cca acc atc Pro Thr Ile 1925	5880
ata aca Ile Thr 1930	gaa gga gaa ggg Glu Gly Glu Gly 1935	aga Arg 1935	gtg atc ctg gga Val Ile Leu Gly 1940	gaa Glu 1940	cca tct gca Pro Ser Ala 1940	5925
gtg aca Val Thr 1945	gca gct agt gcc Ala Ala Ser Ala 1950	gcc Ala 1950	cag aga cgt gga Gln Arg Arg Gly 1955	cgt Arg 1955	atc ggt aga Ile Gly Arg 1955	5970
aat ccg Asn Pro 1960	tcg caa gtt ggt Ser Gln Val Gly 1965	gat Asp 1965	gag tac tgt tat Glu Tyr Cys Tyr 1970	ggg Gly 1970	ggg cac acg Gly His Thr 1970	6015
aat gaa Asn Glu 1975	gac gac tcg aac Asp Asp Ser Asn 1980	ttc Phe 1980	gcc cat tgg act Ala His Trp Thr 1985	gag Glu 1985	gca cga atc Ala Arg Ile 1985	6060
atg ctg Met Leu 1990	gac aac atc aac Asp Asn Ile Asn 1995	atg Met 1995	cca aac gga ctg Pro Asn Gly Leu 2000	atc Ile 2000	gct caa ttc Ala Gln Phe 2000	6105
tac caa Tyr Gln 2005	cca gag cgt gag Pro Glu Arg Glu 2010	aag Lys 2010	gta tat acc atg Val Tyr Thr Met 2015	gat Asp 2015	ggg gaa tac Gly Glu Tyr 2015	6150
cgg ctc Arg Leu 2020	aga gga gaa gag Arg Gly Glu Glu 2025	aga Arg 2025	aaa aac ttt ctg Lys Asn Phe Leu 2030	gaa Glu 2030	ctg ttg agg Leu Leu Arg 2030	6195
act gca Thr Ala 2035	gat ctg cca gtt Asp Leu Pro Val 2040	tgg Trp 2040	ctg gct tac aag Leu Ala Tyr Lys 2045	gtt Val 2045	gca gcg gct Ala Ala Ala 2045	6240
gga gtg Gly Val 2050	tca tac cac gac Ser Tyr His Asp 2055	cgg Arg 2055	agg tgg tgc ttt Arg Trp Cys Phe 2060	gat Asp 2060	ggg cct agg Gly Pro Arg 2060	6285
aca aac Thr Asn 2065	aca att tta gaa Thr Ile Leu Glu 2070	gac Asp 2070	aac aac gaa gtg Asn Asn Glu Val 2075	gaa Glu 2075	gtc atc acg Val Ile Thr 2075	6330
aag ctt Lys Leu 2080	ggg gaa agg aag Gly Glu Arg Lys 2085	att Ile 2085	ctg agg ccg cgc Leu Arg Pro Arg 2090	tgg Trp 2090	att gac gcc Ile Asp Ala 2090	6375
agg gtg Arg Val 2095	tac tcg gat cac Tyr Ser Asp His 2100	cag Gln 2100	gca cta aag gcg Ala Leu Lys Ala 2105	ttc Phe 2105	aag gac ttc Lys Asp Phe 2105	6420
gcc tcg Ala Ser 2110	gga aaa cgt tct Gly Lys Arg Ser 2115	cag Gln 2115	ata ggg ctc att Ile Gly Leu Ile 2120	gag Glu 2120	gtt ctg gga Val Leu Gly 2120	6465
aag atg Lys Met 2125	cct gag cac ttc Pro Glu His Phe 2130	atg Met 2130	ggg aag aca tgg Gly Lys Thr Trp 2135	gaa Glu 2135	gca ctt gac Ala Leu Asp 2135	6510
acc atg Thr Met 2140	tac gtt gtg gcc Tyr Val Val Ala 2145	act Thr 2145	gca gag aaa gga Ala Glu Lys Gly 2150	gga Gly 2150	aga gct cac Arg Ala His 2150	6555
aga atg Arg Met 2155	gcc ctg gag gaa Ala Leu Glu Glu 2160	ctg Leu 2160	cca gat gct ctt Pro Asp Ala Leu 2165	cag Gln 2165	aca att gcc Thr Ile Ala 2165	6600
ttg att Leu Ile 2170	gcc tta ttg agt Ala Leu Leu Ser 2175	gtg Val 2175	atg acc atg gga Met Thr Met Gly 2180	gta Val 2180	ttc ttc ctc Phe Phe Leu 2180	6645

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ctc atg Leu Met 2185	cag cgg aag ggc att Gln Arg Lys Gly Ile 2190	gga aag ata ggt ttg Gly Lys Ile Gly Leu 2195	gga ggc gct Gly Gly Ala 2195	6690
gtc ttg Val Leu 2200	gga gtc gcg acc ttt Gly Val Ala Thr Phe 2205	ttc tgt tgg atg gct Phe Cys Trp Met Ala 2210	gaa gtt cca Glu Val Pro 2210	6735
gga acg Gly Thr 2215	aag atc gcc gga atg Lys Ile Ala Gly Met 2220	ttg ctg ctc tcc ctt Leu Leu Leu Ser Leu 2225	ctc ttg atg Leu Leu Met 2225	6780
att gtg Ile Val 2230	cta att cct gag cca Leu Ile Pro Glu Pro 2235	gag aag caa cgt tcg Glu Lys Gln Arg Ser 2240	cag aca gac Gln Thr Asp 2240	6825
aac cag Asn Gln 2245	cta gcc gtg ttc ctg Leu Ala Val Phe Leu 2250	att tgt gtc atg acc Ile Cys Val Met Thr 2255	ctt gtg agc Leu Val Ser 2255	6870
gca gtg Ala Val 2260	gca gcc aac gag atg Ala Ala Asn Glu Met 2265	ggg tgg cta gat aag Gly Trp Leu Asp Lys 2270	acc aag agt Thr Lys Ser 2270	6915
gac ata Asp Ile 2275	agc agt ttg ttt ggg Ser Ser Leu Phe Gly 2280	caa aga att gag gtc Gln Arg Ile Glu Val 2285	aag gag aat Lys Glu Asn 2285	6960
ttc agc Phe Ser 2290	atg gga gag ttt ctt Met Gly Glu Phe Leu 2295	ttg gac ttg agg cct Leu Asp Leu Arg Pro 2300	gca aca gcc Ala Thr Ala 2300	7005
tgg tca Trp Ser 2305	ctg tac gct gtg aca Leu Tyr Ala Val Thr 2310	aca gcg gtc ctc act Thr Ala Val Leu Thr 2315	cca ctg cta Pro Leu Leu 2315	7050
aag cat Lys His 2320	ttg atc acg tca gat Leu Ile Thr Ser Asp 2325	tac atc aac acc tca Tyr Ile Asn Thr Ser 2330	ttg acc tca Leu Thr Ser 2330	7095
ata aac Ile Asn 2335	gtt cag gca agt gca Val Gln Ala Ser Ala 2340	cta ttc aca ctc gcg Leu Phe Thr Leu Ala 2345	cga ggc ttc Arg Gly Phe 2345	7140
ccc ttc Pro Phe 2350	gtc gat gtt gga gtg Val Asp Val Gly Val 2355	tcg gct ctc ctg cta Ser Ala Leu Leu Leu 2360	gca gcc gga Ala Ala Gly 2360	7185
tgc tgg Cys Trp 2365	gga caa gtc acc ctc Gly Gln Val Thr Leu 2370	acc gtt acg gta aca Thr Val Thr Val Thr 2375	gcg gca aca Ala Ala Thr 2375	7230
ctc ctt Leu Leu 2380	ttt tgc cac tat gcc Phe Cys His Tyr Ala 2385	tac atg gtt ccc ggt Tyr Met Val Pro Gly 2390	tgg caa gct Trp Gln Ala 2390	7275
gag gca Glu Ala 2395	atg cgc tca gcc cag Met Arg Ser Ala Gln 2400	cgg cgg aca gcg gcc Arg Arg Thr Ala Ala 2405	gga atc atg Gly Ile Met 2405	7320
aag aac Lys Asn 2410	gct gta gtg gat ggc Ala Val Val Asp Gly 2415	atc gtg gcc acg gac Ile Val Ala Thr Asp 2420	gtc cca gaa Val Pro Glu 2420	7365
tta gag Leu Glu 2425	cgc acc aca ccc atc Arg Thr Thr Pro Ile 2430	atg cag aag aaa gtt Met Gln Lys Lys Val 2435	gga cag atc Gly Gln Ile 2435	7410
atg ctg Met Leu 2440	atc ttg gtg tct cta Ile Leu Val Ser Leu 2445	gct gca gta gta gtg Ala Ala Val Val Val 2450	aac ccg tct Asn Pro Ser 2450	7455
gtg aag Val Lys 2455	aca gta cga gaa gcc Thr Val Arg Glu Ala 2460	gga att ttg atc acg Gly Ile Leu Ile Thr 2465	gcc gca gcg Ala Ala Ala 2465	7500
gtg acg Val Thr 2470	ctt tgg gag aat gga Leu Trp Glu Asn Gly 2475	gca agc tct gtt tgg Ala Ser Ser Val Trp 2480	aac gca aca Asn Ala Thr 2480	7545

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act gcc Thr Ala 2485	atc gga ctc tgc Ile Gly Leu Cys 2490	cac His 2490	atc atg cgt ggg Ile Met Arg Gly 2495	ggt Gly 2495	tgg ttg tca Trp Leu Ser 2500	7590
tgt cta Cys Leu 2500	tcc ata aca tgg Ser Ile Thr Trp 2505	aca Thr 2505	ctc ata aag aac Leu Ile Lys Asn 2510	atg Met 2510	gaa aaa cca Glu Lys Pro 2515	7635
gga cta Gly Leu 2515	aaa aga ggt ggg Lys Arg Gly Gly 2520	gca Ala 2520	aaa gga cgc acc Lys Gly Arg Thr 2525	ttg Leu 2525	gga gag gtt Gly Glu Val 2530	7680
tgg aaa Trp Lys 2530	gaa aga ctc aac Glu Arg Leu Asn 2535	cag Gln 2535	atg aca aaa gaa Met Thr Lys Glu 2540	gag Glu 2540	ttc act agg Phe Thr Arg 2545	7725
tac cgc Tyr Arg 2545	aaa gag gcc atc Lys Glu Ala Ile 2550	atc Ile 2550	gaa gtc gat cgc Glu Val Asp Arg 2555	tca Ser 2555	gcg gca aaa Ala Ala Lys 2560	7770
cac gcc His Ala 2560	agg aaa gaa ggc Arg Lys Glu Gly 2565	aat Asn 2565	gtc act gga ggg Val Thr Gly Gly 2570	cat His 2570	cca gtc tct Pro Val Ser 2575	7815
agg ggc Arg Gly 2575	aca gca aaa ctg Thr Ala Lys Leu 2580	aga Arg 2580	tgg ctg gtc gaa Trp Leu Val Glu 2585	cgg Arg 2585	agg ttt ctc Arg Phe Leu 2590	7860
gaa ccg Glu Pro 2590	gtc gga aaa gtg Val Gly Lys Val 2595	att Ile 2595	gac ctt gga tgt Asp Leu Gly Cys 2600	gga Gly 2600	aga ggc ggt Arg Gly Gly 2605	7905
tgg tgt Trp Cys 2605	tac tat atg gca Tyr Tyr Met Ala 2610	acc Thr 2610	caa aaa aga gtc Gln Lys Arg Val 2615	caa Gln 2615	gaa gtc aga Glu Val Arg 2620	7950
ggg tac Gly Tyr 2620	aca aag ggc ggt Thr Lys Gly Gly 2625	ccc Pro 2625	gga cat gaa gag Gly His Glu Glu 2630	ccc Pro 2630	caa cta gtg Gln Leu Val 2635	7995
caa agt Gln Ser 2635	tat gga tgg aac Tyr Gly Trp Asn 2640	att Ile 2640	gtc acc atg aag Val Thr Met Lys 2645	agt Ser 2645	gga gtg gat Gly Val Asp 2650	8040
gtg ttc Val Phe 2650	tac aga cct tct Tyr Arg Pro Ser 2655	gag Glu 2655	tgt tgt gac acc Cys Cys Asp Thr 2660	ctc Leu 2660	ctt tgt gac Leu Cys Asp 2665	8085
atc gga Ile Gly 2665	gag tcc tcg tca Glu Ser Ser Ser 2670	agt Ser 2670	gct gag gtt gaa Ala Glu Val Glu 2675	gag Glu 2675	cat agg acg His Arg Thr 2680	8130
att cgg Ile Arg 2680	gtc ctt gaa atg Val Leu Glu Met 2685	gtt Val 2685	gag gac tgg ctg Glu Asp Trp Leu 2690	cac His 2690	cga ggg cca Arg Gly Pro 2695	8175
agg gaa Arg Glu 2695	ttt tgc gtg aag Phe Cys Val Lys 2700	gtg Val 2700	ctc tgc ccc tac Leu Cys Pro Tyr 2705	atg Met 2705	ccg aaa gtc Pro Lys Val 2710	8220
ata gag Ile Glu 2710	aag atg gag ctg Lys Met Glu Leu 2715	ctc Leu 2715	caa cgc cgg tat Gln Arg Arg Tyr 2720	ggg Gly 2720	ggg gga ctg Gly Gly Leu 2725	8265
gtc aga Val Arg 2725	aac cca ctc tca Asn Pro Leu Ser 2730	cgg Arg 2730	aat tcc acg cac Asn Ser Thr His 2735	gag Glu 2735	atg tat tgg Met Tyr Trp 2740	8310
gtg agt Val Ser 2740	cga gct tca ggc Arg Ala Ser Gly 2745	aat Asn 2745	gtg gta cat tca Val Val His Ser 2750	gtg Val 2750	aat atg acc Asn Met Thr 2755	8355
agc cag Ser Gln 2755	gtg ctc cta gga Val Leu Leu Gly 2760	aga Arg 2760	atg gaa aaa agg Met Glu Lys Arg 2765	acc Thr 2765	tgg aag gga Trp Lys Gly 2770	8400
ccc caa Pro Gln 2770	tac gag gaa gat Tyr Glu Glu Asp 2775	gta Val 2775	aac ttg gga agt Asn Leu Gly Ser 2780	gga Gly 2780	acc agg gcg Thr Arg Ala 2785	8445

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gtg gga	aaa ccc ctg ctc aac	tca gac acc agt aaa	atc aag aac	8490
Val Gly	Lys Pro Leu Leu Asn	Ser Asp Thr Ser Lys	Ile Lys Asn	
2785	2790	2795		
agg att	gaa cga ctc agg cgt	gag tac agt tcg acg	tgg cac cac	8535
Arg Ile	Glu Arg Leu Arg Arg	Glu Tyr Ser Ser Thr	Trp His His	
2800	2805	2810		
gat gag	aac cac cca tat aga	acc tgg aac tat cac	ggc agt tat	8580
Asp Glu	Asn His Pro Tyr Arg	Thr Trp Asn Tyr His	Gly Ser Tyr	
2815	2820	2825		
gat gtg	aag ccc aca ggc tcc	gcc agt tcg ctg gtc	aat gga gtg	8625
Asp Val	Lys Pro Thr Gly Ser	Ala Ser Ser Leu Val	Asn Gly Val	
2830	2835	2840		
gtc agg	ctc ctc tca aaa cca	tgg gac acc atc acg	aat gtt acc	8670
Val Arg	Leu Leu Ser Lys Pro	Trp Asp Thr Ile Thr	Asn Val Thr	
2845	2850	2855		
acc atg	gcc atg act gac act	act ccc ttc ggg cag	cag cga gtg	8715
Thr Met	Ala Met Thr Asp Thr	Thr Pro Phe Gly Gln	Gln Arg Val	
2860	2865	2870		
ttc aaa	gag aag gtg gac acg	aaa gct cct gaa ccg	cca gaa gga	8760
Phe Lys	Glu Lys Val Asp Thr	Lys Ala Pro Glu Pro	Pro Glu Gly	
2875	2880	2885		
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Val Lys	Tyr Val Leu Asn Glu	Thr Thr Asn Trp Leu	Trp Ala Phe	
2890	2895	2900		
ttg gcc	aga gaa aaa cgt ccc	aga atg tgc tct cga	gag gaa ttc	8850
Leu Ala	Arg Glu Lys Arg Pro	Arg Met Cys Ser Arg	Glu Glu Phe	
2905	2910	2915		
ata aga	aag gtc aac agc aat	gca gct ttg ggt gcc	atg ttt gaa	8895
Ile Arg	Lys Val Asn Ser Asn	Ala Ala Leu Gly Ala	Met Phe Glu	
2920	2925	2930		
gag cag	aat caa tgg agg agc	gcc aga gaa gca gtt	gaa gat cca	8940
Glu Gln	Asn Gln Trp Arg Ser	Ala Arg Glu Ala Val	Glu Asp Pro	
2935	2940	2945		
aaa ttt	tgg gag atg gtg gat	gag gag cgc gag gca	cat ctg cgg	8985
Lys Phe	Trp Glu Met Val Asp	Glu Glu Arg Glu Ala	His Leu Arg	
2950	2955	2960		
ggg gaa	tgt cac act tgc att	tac aac atg atg gga	aag aga gag	9030
Gly Glu	Cys His Thr Cys Ile	Tyr Asn Met Met Gly	Lys Arg Glu	
2965	2970	2975		
aaa aaa	ccc gga gag ttc gga	aag gcc aag gga agc	aga gcc att	9075
Lys Lys	Pro Gly Glu Phe Gly	Lys Ala Lys Gly Ser	Arg Ala Ile	
2980	2985	2990		
tgg ttc	atg tgg ctc gga gct	cgc ttt ctg gag ttc	gag gct ctg	9120
Trp Phe	Met Trp Leu Gly Ala	Arg Phe Leu Glu Phe	Glu Ala Leu	
2995	3000	3005		
ggg ttt	ctc aat gaa gac cac	tgg ctt gga aga aag	aac tca gga	9165
Gly Phe	Leu Asn Glu Asp His	Trp Leu Gly Arg Lys	Asn Ser Gly	
3010	3015	3020		
gga ggt	gtc gag ggc ttg ggc	ctc caa aaa ctg ggt	tac atc ctg	9210
Gly Gly	Val Glu Gly Leu Gly	Leu Gln Lys Leu Gly	Tyr Ile Leu	
3025	3030	3035		
cgt gaa	gtt ggc acc cgg cct	ggg ggc aag atc tat	gct gat gac	9255
Arg Glu	Val Gly Thr Arg Pro	Gly Gly Lys Ile Tyr	Ala Asp Asp	
3040	3045	3050		
aca gct	ggc tgg gac acc cgc	atc acg aga gct gac	ttg gaa aat	9300
Thr Ala	Gly Trp Asp Thr Arg	Ile Thr Arg Ala Asp	Leu Glu Asn	
3055	3060	3065		
gaa gct	aag gtg ctt gag ctg	ctt gat ggg gaa cat	cgg cgt ctt	9345
Glu Ala	Lys Val Leu Glu Leu	Leu Asp Gly Glu His	Arg Arg Leu	
3070	3075	3080		

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gcc agg Ala Arg 3085	gcc atc att gag Ala Ile Ile Glu 3090	ctc Leu 3090	acc tat cgt cac Thr Tyr Arg His 3095	aaa gtt gtg aaa Lys Val Val Lys 3095	9390
gtg atg Val Met 3100	cgc ccg gct gct Arg Pro Ala Ala 3105	gat Asp 3105	gga aga acc gtc Gly Arg Thr Val 3110	atg gat gtt atc Met Asp Val Ile 3110	9435
tcc aga Ser Arg 3115	gaa gat cag agg Glu Asp Gln Arg 3120	ggg Gly 3120	agt gga caa gtt Ser Gly Gln Val 3125	gtc acc tac gcc Val Thr Tyr Ala 3125	9480
cta aac Leu Asn 3130	act ttc acc aac Thr Phe Thr Asn 3135	ctg Leu 3135	gcc gtc cag ctg Ala Val Gln Leu 3140	gtg agg atg atg Val Arg Met Met 3140	9525
gaa ggg Glu Gly 3145	gaa gga gtg att Glu Gly Val Ile 3150	ggc Gly 3150	cca gat gat gtg Pro Asp Asp Val 3155	gag aaa ctc aca Glu Lys Leu Thr 3155	9570
aaa ggg Lys Gly 3160	aaa gga ccc aaa Lys Gly Pro Lys 3165	gtc Val 3165	agg acc tgg ctg Arg Thr Trp Leu 3170	ttt gag aat ggg Phe Glu Asn Gly 3170	9615
gaa gaa Glu Glu 3175	aga ctc agc cgc Arg Leu Ser Arg 3180	atg Met 3180	gct gtc agt gga Ala Val Ser Gly 3185	gat gac tgt gtg Asp Asp Cys Val 3185	9660
gta aag Val Lys 3190	ccc ctg gac gat Pro Leu Asp Asp 3195	cgc Arg 3195	ttt gcc acc tcg Phe Ala Thr Ser 3200	ctc cac ttc ctc Leu His Phe Leu 3200	9705
aat gct Asn Ala 3205	atg tca aag gtt Met Ser Lys Val 3210	cgc Arg 3210	aaa gac atc caa Lys Asp Ile Gln 3215	gag tgg aaa ccg Glu Trp Lys Pro 3215	9750
tca act Ser Thr 3220	gga tgg tat gat Gly Trp Tyr Asp 3225	tgg Trp 3225	cag cag gtt cca Gln Gln Val Pro 3230	ttt tgc tca aac Phe Cys Ser Asn 3230	9795
cat ttc His Phe 3235	act gaa ttg atc Thr Glu Leu Ile 3240	atg Met 3240	aaa gat gga aga Lys Asp Gly Arg 3245	aca ctg gtg gtt Thr Leu Val Val 3245	9840
cca tgc Pro Cys 3250	cga gga cag gat Arg Gly Gln Asp 3255	gaa Glu 3255	ttg gta ggc aga Leu Val Gly Arg 3260	gct cgc ata tct Ala Arg Ile Ser 3260	9885
cca ggg Pro Gly 3265	gcc gga tgg aac Ala Gly Trp Asn 3270	gtc Val 3270	cgc gac act gct Arg Asp Thr Ala 3275	tgt ctg gct aag Cys Leu Ala Lys 3275	9930
tct tat Ser Tyr 3280	gcc cag atg tgg Ala Gln Met Trp 3285	ctg Leu 3285	ctt ctg tac ttc Leu Leu Tyr Phe 3290	cac aga aga gac His Arg Arg Asp 3290	9975
ctg cgg Leu Arg 3295	ctc atg gcc aac Leu Met Ala Asn 3300	gcc Ala 3300	att tgc tcc gct Ile Cys Ser Ala 3305	gtc cct gtg aat Val Pro Val Asn 3305	10020
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tgg ata Trp Ile 3340	gag gag aat gaa Glu Glu Asn Glu 3345	tgg Trp 3345	atg gaa gac aaa Met Glu Asp Lys 3350	acc cca gtg gag Thr Pro Val Glu 3350	10155
aaa tgg Lys Trp 3355	agt gac gtc cca Ser Asp Val Pro 3360	tat Tyr 3360	tca gga aaa cga Ser Gly Lys Arg 3365	gag gac atc tgg Glu Asp Ile Trp 3365	10200
tgt ggc Cys Gly 3370	agc ctg att ggc Ser Leu Ile Gly 3375	aca Thr 3375	aga gcc cga gcc Arg Ala Arg Ala 3380	acg tgg gca gaa Thr Trp Ala Glu 3380	10245

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Asn Ile  Gln Val Ala Ile Asn  Gln Val Arg Ala Ile  Ile Gly Asp
3385                      3390                      3395

gag aag  tat gtg gat tac atg  agt tca cta aag aga  tat gaa gac      10335
Glu Lys  Tyr Val Asp Tyr Met  Ser Ser Leu Lys Arg  Tyr Glu Asp
3400                      3405                      3410

aca act  ttg gtt gag gac aca  gta ctg tagatatatta atcaattgta      10382
Thr Thr  Leu Val Glu Asp Thr  Val Leu
3415                      3420

aatagacaat ataagtatgc ataaaagtgt agttttatag tagtatttag tgggtgtagt  10442

gtaaatagtt aagaaaattt tgaggagaaa gtcaggccgg gaagttcccg ccaccggaag  10502

ttgagttagc ggtgctgcct gcgactcaac cccaggagga ctgggtgaac aaagccgcga  10562

agtgatccat gtaagccctc agaaccgtct cggaaggagg accccacatg ttgtaacttc  10622

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gtgccccagg aggactgggt taacaaaggc aaaccaacgc cccacgcggc cctagccccg  10742

gtaatggtgt taaccagggc gaaaggacta gaggttagag gagacccgcg ggtttaaagt  10802

gcacggccca gcctggtctga agctgtaggt caggggaagg actagagggt agtggagacc  10862

ccgtgccaca aaacaccaca acaaaacagc atattgacac ctgggataga ctaggagatc  10922

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<210> SEQ ID NO 2
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

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<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 Ser Ala Gly Met Ile Ile Met
100         105         110

Leu Ile Pro Thr Val Met Ala Phe His Leu Thr Thr Arg Asn Gly Glu
115         120         125

Pro His Met Ile Val Ser Arg Gln Glu Lys Gly Lys Ser Leu Leu Phe
130         135         140

Lys Thr Glu Asp Gly Val Asn Met Cys Thr Leu Met Ala Met Asp Leu
145         150         155         160

Gly Glu Leu Cys Glu Asp Thr Ile Thr Tyr Lys Cys Pro Leu Leu Arg
165         170         175

Gln Asn Glu Pro Glu Asp Ile Asp Cys Trp Cys Asn Ser Thr Ser Thr
180         185         190

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Trp	Val	Thr	Tyr	Gly	Thr	Cys	Thr	Thr	Met	Gly	Glu	His	Arg	Arg	Glu
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Lys	Arg	Ser	Val	Ala	Leu	Val	Pro	His	Val	Gly	Met	Gly	Leu	Glu	Thr
	210					215					220				
Arg	Thr	Glu	Thr	Trp	Met	Ser	Ser	Glu	Gly	Ala	Trp	Lys	His	Val	Gln
225					230					235					240
Arg	Ile	Glu	Thr	Trp	Ile	Leu	Arg	His	Pro	Gly	Phe	Thr	Met	Met	Ala
				245					250					255	
Ala	Ile	Leu	Ala	Tyr	Thr	Ile	Gly	Thr	Thr	His	Phe	Gln	Arg	Ala	Leu
			260					265					270		
Ile	Phe	Ile	Leu	Leu	Thr	Ala	Val	Thr	Pro	Ser	Met	Thr	Met	Arg	Cys
	275						280					285			
Ile	Gly	Met	Ser	Asn	Arg	Asp	Phe	Val	Glu	Gly	Val	Ser	Gly	Gly	Ser
	290					295					300				
Trp	Val	Asp	Ile	Val	Leu	Glu	His	Gly	Ser	Cys	Val	Thr	Thr	Met	Ala
305					310					315					320
Lys	Asn	Lys	Pro	Thr	Leu	Asp	Phe	Glu	Leu	Ile	Lys	Thr	Glu	Ala	Lys
				325					330					335	
Gln	Pro	Ala	Thr	Leu	Arg	Lys	Tyr	Cys	Ile	Glu	Ala	Lys	Leu	Thr	Asn
			340					345					350		
Thr	Thr	Thr	Glu	Ser	Arg	Cys	Pro	Thr	Gln	Gly	Glu	Pro	Ser	Leu	Asn
		355					360					365			
Glu	Glu	Gln	Asp	Lys	Arg	Phe	Val	Cys	Lys	His	Ser	Met	Val	Asp	Arg
	370					375					380				
Gly	Trp	Gly	Asn	Gly	Cys	Gly	Leu	Phe	Gly	Lys	Gly	Gly	Ile	Val	Thr
385					390					395					400
Cys	Ala	Met	Phe	Arg	Cys	Lys	Lys	Asn	Met	Glu	Gly	Lys	Val	Val	Gln
				405					410					415	
Pro	Glu	Asn	Leu	Glu	Tyr	Thr	Ile	Val	Ile	Thr	Pro	His	Ser	Gly	Glu
			420					425					430		
Glu	His	Ala	Val	Gly	Asn	Asp	Thr	Gly	Lys	His	Gly	Lys	Glu	Ile	Lys
		435					440					445			
Ile	Thr	Pro	Gln	Ser	Ser	Ile	Thr	Glu	Ala	Glu	Leu	Thr	Gly	Tyr	Gly
	450					455					460				
Thr	Val	Thr	Met	Glu	Cys	Ser	Pro	Arg	Thr	Gly	Leu	Asp	Phe	Asn	Glu
465					470					475					480
Met	Val	Leu	Leu	Gln	Met	Glu	Asn	Lys	Ala	Trp	Leu	Val	His	Arg	Gln
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Trp	Phe	Leu	Asp	Leu	Pro	Leu	Pro	Trp	Leu	Pro	Gly	Ala	Asp	Thr	Gln
		500						505					510		
Gly	Ser	Asn	Trp	Ile	Gln	Lys	Glu	Thr	Leu	Val	Thr	Phe	Lys	Asn	Pro
		515					520					525			
His	Ala	Lys	Lys	Gln	Asp	Val	Val	Val	Leu	Gly	Ser	Gln	Glu	Gly	Ala
	530					535					540				
Met	His	Thr	Ala	Leu	Thr	Gly	Ala	Thr	Glu	Ile	Gln	Met	Ser	Ser	Gly
545					550				555						560
Asn	Leu	Leu	Phe	Thr	Gly	His	Leu	Lys	Cys	Arg	Leu	Arg	Met	Asp	Lys
				565					570					575	
Leu	Gln	Leu	Lys	Gly	Met	Ser	Tyr	Ser	Met	Cys	Thr	Gly	Lys	Phe	Lys
			580					585					590		
Val	Val	Lys	Glu	Ile	Ala	Glu	Thr	Gln	His	Gly	Thr	Ile	Val	Ile	Arg
		595					600					605			
Val	Gln	Tyr	Glu	Gly	Asp	Gly	Ser	Pro	Cys	Lys	Ile	Pro	Phe	Glu	Ile
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Met	Asp	Leu	Glu	Lys	Arg	His	Val	Leu	Gly	Arg	Leu	Ile	Thr	Val	Asn	625	630	635	640
Pro	Ile	Val	Thr	Glu	Lys	Asp	Ser	Pro	Val	Asn	Ile	Glu	Ala	Glu	Pro	645	650	655	
Pro	Phe	Gly	Asp	Ser	Tyr	Ile	Ile	Ile	Gly	Val	Glu	Pro	Gly	Gln	Leu	660	665	670	
Lys	Leu	Asn	Trp	Phe	Lys	Lys	Gly	Ser	Ser	Ile	Gly	Gln	Met	Phe	Glu	675	680	685	
Thr	Thr	Met	Arg	Gly	Ala	Lys	Arg	Met	Ala	Ile	Leu	Gly	Asp	Thr	Ala	690	695	700	
Trp	Asp	Phe	Gly	Ser	Leu	Gly	Gly	Val	Phe	Thr	Ser	Ile	Gly	Lys	Ala	705	710	715	720
Leu	His	Gln	Val	Phe	Gly	Ala	Ile	Tyr	Gly	Ala	Ala	Phe	Ser	Gly	Val	725	730	735	
Ser	Trp	Thr	Met	Lys	Ile	Leu	Ile	Gly	Val	Ile	Ile	Thr	Trp	Ile	Gly	740	745	750	
Met	Asn	Ser	Arg	Ser	Thr	Ser	Leu	Ser	Val	Thr	Leu	Val	Leu	Val	Gly	755	760	765	
Ile	Val	Thr	Leu	Tyr	Leu	Gly	Val	Met	Val	Gln	Ala	Asp	Ser	Gly	Cys	770	775	780	
Ala	Ile	Asp	Ile	Ser	Arg	Gln	Glu	Leu	Arg	Cys	Gly	Ser	Gly	Val	Phe	785	790	795	800
Ile	His	Asn	Asp	Val	Glu	Ala	Trp	Met	Asp	Arg	Tyr	Lys	Tyr	Tyr	Pro	805	810	815	
Glu	Thr	Pro	Gln	Gly	Leu	Ala	Lys	Ile	Ile	Gln	Lys	Ala	His	Lys	Glu	820	825	830	
Gly	Val	Cys	Gly	Leu	Arg	Ser	Val	Ser	Arg	Leu	Glu	His	Gln	Met	Trp	835	840	845	
Glu	Ala	Val	Lys	Asp	Glu	Leu	Asn	Thr	Leu	Leu	Lys	Glu	Asn	Gly	Val	850	855	860	
Asp	Leu	Ser	Val	Val	Val	Glu	Lys	Gln	Glu	Gly	Met	Tyr	Lys	Ser	Ala	865	870	875	880
Pro	Lys	Arg	Leu	Thr	Ala	Thr	Thr	Glu	Lys	Leu	Glu	Ile	Gly	Trp	Lys	885	890	895	
Ala	Trp	Gly	Lys	Ser	Ile	Leu	Phe	Ala	Pro	Glu	Leu	Ala	Asn	Asn	Thr	900	905	910	
Phe	Val	Val	Asp	Gly	Pro	Glu	Thr	Lys	Glu	Cys	Pro	Thr	Gln	Asn	Arg	915	920	925	
Ala	Trp	Asn	Ser	Leu	Glu	Val	Glu	Asp	Phe	Gly	Phe	Gly	Leu	Thr	Ser	930	935	940	
Thr	Arg	Met	Phe	Leu	Lys	Val	Arg	Glu	Ser	Asn	Thr	Thr	Glu	Cys	Asp	945	950	955	960
Ser	Lys	Ile	Ile	Gly	Thr	Ala	Val	Lys	Asn	Asn	Leu	Ala	Ile	His	Ser	965	970	975	
Asp	Leu	Ser	Tyr	Trp	Ile	Glu	Ser	Arg	Leu	Asn	Asp	Thr	Trp	Lys	Leu	980	985	990	
Glu	Arg	Ala	Val	Leu	Gly	Glu	Val	Lys	Ser	Cys	Thr	Trp	Pro	Glu	Thr	995	1000	1005	
His	Thr	Leu	Trp	Gly	Asp	Gly	Ile	Leu	Glu	Ser	Asp	Leu	Ile	Ile		1010	1015	1020	
Pro	Val	Thr	Leu	Ala	Gly	Pro	Arg	Ser	Asn	His	Asn	Arg	Arg	Pro		1025	1030	1035	
Gly	Tyr	Lys	Thr	Gln	Asn	Gln	Gly	Pro	Trp	Asp	Glu	Gly	Arg	Val					

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1040	1045	1050
Glu Ile Asp Phe Asp Tyr Cys Pro Gly Thr Thr Val Thr Leu Ser		
1055	1060	1065
Glu Ser Cys Gly His Arg Gly Pro Ala Thr Arg Thr Thr Thr Glu		
1070	1075	1080
Ser Gly Lys Leu Ile Thr Asp Trp Cys Cys Arg Ser Cys Thr Leu		
1085	1090	1095
Pro Pro Leu Arg Tyr Gln Thr Asp Ser Gly Cys Trp Tyr Gly Met		
1100	1105	1110
Glu Ile Arg Pro Gln Arg His Asp Glu Lys Thr Leu Val Gln Ser		
1115	1120	1125
Gln Val Asn Ala Tyr Asn Ala Asp Met Ile Asp Pro Phe Gln Leu		
1130	1135	1140
Gly Leu Leu Val Val Phe Leu Ala Thr Gln Glu Val Leu Arg Lys		
1145	1150	1155
Arg Trp Thr Ala Lys Ile Ser Met Pro Ala Ile Leu Ile Ala Leu		
1160	1165	1170
Leu Val Leu Val Phe Gly Gly Ile Thr Tyr Thr Asp Val Leu Arg		
1175	1180	1185
Tyr Val Ile Leu Val Gly Ala Ala Phe Ala Glu Ser Asn Ser Gly		
1190	1195	1200
Gly Asp Val Val His Leu Ala Leu Met Ala Thr Phe Lys Ile Gln		
1205	1210	1215
Pro Val Phe Met Val Ala Ser Phe Leu Lys Ala Arg Trp Thr Asn		
1220	1225	1230
Gln Glu Asn Ile Leu Leu Met Leu Ala Ala Val Phe Phe Gln Met		
1235	1240	1245
Ala Tyr Tyr Asp Ala Arg Gln Ile Leu Leu Trp Glu Ile Pro Asp		
1250	1255	1260
Val Leu Asn Ser Leu Ala Val Ala Trp Met Ile Leu Arg Ala Ile		
1265	1270	1275
Thr Phe Thr Thr Thr Ser Asn Val Val Val Pro Leu Leu Ala Leu		
1280	1285	1290
Leu Thr Pro Gly Leu Arg Cys Leu Asn Leu Asp Val Tyr Arg Ile		
1295	1300	1305
Leu Leu Leu Met Val Gly Ile Gly Ser Leu Ile Arg Glu Lys Arg		
1310	1315	1320
Ser Ala Ala Ala Lys Lys Lys Gly Ala Ser Leu Leu Cys Leu Ala		
1325	1330	1335
Leu Ala Ser Thr Gly Leu Phe Asn Pro Met Ile Leu Ala Ala Gly		
1340	1345	1350
Leu Ile Ala Cys Asp Pro Asn Arg Lys Arg Gly Trp Pro Ala Thr		
1355	1360	1365
Glu Val Met Thr Ala Val Gly Leu Met Phe Ala Ile Val Gly Gly		
1370	1375	1380
Leu Ala Glu Leu Asp Ile Asp Ser Met Ala Ile Pro Met Thr Ile		
1385	1390	1395
Ala Gly Leu Met Phe Ala Ala Phe Val Ile Ser Gly Lys Ser Thr		
1400	1405	1410
Asp Met Trp Ile Glu Arg Thr Ala Asp Ile Ser Trp Glu Ser Asp		
1415	1420	1425
Ala Glu Ile Thr Gly Ser Ser Glu Arg Val Asp Val Arg Leu Asp		
1430	1435	1440

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Asp	Asp	Gly	Asn	Phe	Gln	Leu	Met	Asn	Asp	Pro	Gly	Ala	Pro	Trp
1445						1450					1455			
Lys	Ile	Trp	Met	Leu	Arg	Met	Val	Cys	Leu	Ala	Ile	Ser	Ala	Tyr
1460						1465					1470			
Thr	Pro	Trp	Ala	Ile	Leu	Pro	Ser	Val	Val	Gly	Phe	Trp	Ile	Thr
1475						1480					1485			
Leu	Gln	Tyr	Thr	Lys	Arg	Gly	Gly	Val	Leu	Trp	Asp	Thr	Pro	Ser
1490						1495					1500			
Pro	Lys	Glu	Tyr	Lys	Lys	Gly	Asp	Thr	Thr	Thr	Gly	Val	Tyr	Arg
1505						1510					1515			
Ile	Met	Thr	Arg	Gly	Leu	Leu	Gly	Ser	Tyr	Gln	Ala	Gly	Ala	Gly
1520						1525					1530			
Val	Met	Val	Glu	Gly	Val	Phe	His	Thr	Leu	Trp	His	Thr	Thr	Lys
1535						1540					1545			
Gly	Ala	Ala	Leu	Met	Ser	Gly	Glu	Gly	Arg	Leu	Asp	Pro	Tyr	Trp
1550						1555					1560			
Gly	Ser	Val	Lys	Glu	Asp	Arg	Leu	Cys	Tyr	Gly	Gly	Pro	Trp	Lys
1565						1570					1575			
Leu	Gln	His	Lys	Trp	Asn	Gly	Gln	Asp	Glu	Val	Gln	Met	Ile	Val
1580						1585					1590			
Val	Glu	Pro	Gly	Arg	Asn	Val	Lys	Asn	Val	Gln	Thr	Lys	Pro	Gly
1595						1600					1605			
Val	Phe	Lys	Thr	Pro	Glu	Gly	Glu	Ile	Gly	Ala	Val	Thr	Leu	Asp
1610						1615					1620			
Phe	Pro	Thr	Gly	Thr	Ser	Gly	Ser	Pro	Ile	Val	Asp	Lys	Asn	Gly
1625						1630					1635			
Asp	Val	Ile	Gly	Leu	Tyr	Gly	Asn	Gly	Val	Ile	Met	Pro	Asn	Gly
1640						1645					1650			
Ser	Tyr	Ile	Ser	Ala	Ile	Val	Gln	Gly	Glu	Arg	Met	Asp	Glu	Pro
1655						1660					1665			
Ile	Pro	Ala	Gly	Phe	Glu	Pro	Glu	Met	Leu	Arg	Lys	Lys	Gln	Ile
1670						1675					1680			
Thr	Val	Leu	Asp	Leu	His	Pro	Gly	Ala	Gly	Lys	Thr	Arg	Arg	Ile
1685						1690					1695			
Leu	Pro	Gln	Ile	Ile	Lys	Glu	Ala	Ile	Asn	Arg	Arg	Leu	Arg	Thr
1700						1705					1710			
Ala	Val	Leu	Ala	Pro	Thr	Arg	Val	Val	Ala	Ala	Glu	Met	Ala	Glu
1715						1720					1725			
Ala	Leu	Arg	Gly	Leu	Pro	Ile	Arg	Tyr	Gln	Thr	Ser	Ala	Val	Pro
1730						1735					1740			
Arg	Glu	His	Asn	Gly	Asn	Glu	Ile	Val	Asp	Val	Met	Cys	His	Ala
1745						1750					1755			
Thr	Leu	Thr	His	Arg	Leu	Met	Ser	Pro	His	Arg	Val	Pro	Asn	Tyr
1760						1765					1770			
Asn	Leu	Phe	Val	Met	Asp	Glu	Ala	His	Phe	Thr	Asp	Pro	Ala	Ser
1775						1780					1785			
Ile	Ala	Ala	Arg	Gly	Tyr	Ile	Ser	Thr	Lys	Val	Glu	Leu	Gly	Glu
1790						1795					1800			
Ala	Ala	Ala	Ile	Phe	Met	Thr	Ala	Thr	Pro	Pro	Gly	Thr	Ser	Asp
1805						1810					1815			
Pro	Phe	Pro	Glu	Ser	Asn	Ser	Pro	Ile	Ser	Asp	Leu	Gln	Thr	Glu
1820						1825					1830			
Ile	Pro	Asp	Arg	Ala	Trp	Asn	Ser	Gly	Tyr	Glu	Trp	Ile	Thr	Glu
1835						1840					1845			

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Tyr Thr	Gly Lys Thr Val Trp	Phe Val Pro Ser Val	Lys Met Gly
1850	1855	1860	
Asn Glu	Ile Ala Leu Cys Leu	Gln Arg Ala Gly Lys	Lys Val Val
1865	1870	1875	
Gln Leu	Asn Arg Lys Ser Tyr	Glu Thr Glu Tyr Pro	Lys Cys Lys
1880	1885	1890	
Asn Asp	Asp Trp Asp Phe Val	Ile Thr Thr Asp Ile	Ser Glu Met
1895	1900	1905	
Gly Ala	Asn Phe Lys Ala Ser	Arg Val Ile Asp Ser	Arg Lys Ser
1910	1915	1920	
Val Lys	Pro Thr Ile Ile Thr	Glu Gly Glu Gly Arg	Val Ile Leu
1925	1930	1935	
Gly Glu	Pro Ser Ala Val Thr	Ala Ala Ser Ala Ala	Gln Arg Arg
1940	1945	1950	
Gly Arg	Ile Gly Arg Asn Pro	Ser Gln Val Gly Asp	Glu Tyr Cys
1955	1960	1965	
Tyr Gly	Gly His Thr Asn Glu	Asp Asp Ser Asn Phe	Ala His Trp
1970	1975	1980	
Thr Glu	Ala Arg Ile Met Leu	Asp Asn Ile Asn Met	Pro Asn Gly
1985	1990	1995	
Leu Ile	Ala Gln Phe Tyr Gln	Pro Glu Arg Glu Lys	Val Tyr Thr
2000	2005	2010	
Met Asp	Gly Glu Tyr Arg Leu	Arg Gly Glu Glu Arg	Lys Asn Phe
2015	2020	2025	
Leu Glu	Leu Leu Arg Thr Ala	Asp Leu Pro Val Trp	Leu Ala Tyr
2030	2035	2040	
Lys Val	Ala Ala Ala Gly Val	Ser Tyr His Asp Arg	Arg Trp Cys
2045	2050	2055	
Phe Asp	Gly Pro Arg Thr Asn	Thr Ile Leu Glu Asp	Asn Asn Glu
2060	2065	2070	
Val Glu	Val Ile Thr Lys Leu	Gly Glu Arg Lys Ile	Leu Arg Pro
2075	2080	2085	
Arg Trp	Ile Asp Ala Arg Val	Tyr Ser Asp His Gln	Ala Leu Lys
2090	2095	2100	
Ala Phe	Lys Asp Phe Ala Ser	Gly Lys Arg Ser Gln	Ile Gly Leu
2105	2110	2115	
Ile Glu	Val Leu Gly Lys Met	Pro Glu His Phe Met	Gly Lys Thr
2120	2125	2130	
Trp Glu	Ala Leu Asp Thr Met	Tyr Val Val Ala Thr	Ala Glu Lys
2135	2140	2145	
Gly Gly	Arg Ala His Arg Met	Ala Leu Glu Glu Leu	Pro Asp Ala
2150	2155	2160	
Leu Gln	Thr Ile Ala Leu Ile	Ala Leu Leu Ser Val	Met Thr Met
2165	2170	2175	
Gly Val	Phe Phe Leu Leu Met	Gln Arg Lys Gly Ile	Gly Lys Ile
2180	2185	2190	
Gly Leu	Gly Gly Ala Val Leu	Gly Val Ala Thr Phe	Phe Cys Trp
2195	2200	2205	
Met Ala	Glu Val Pro Gly Thr	Lys Ile Ala Gly Met	Leu Leu Leu
2210	2215	2220	
Ser Leu	Leu Leu Met Ile Val	Leu Ile Pro Glu Pro	Glu Lys Gln
2225	2230	2235	
Arg Ser	Gln Thr Asp Asn Gln	Leu Ala Val Phe Leu	Ile Cys Val

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2240	2245	2250
Met Thr Leu Val Ser Ala Val	Ala Ala Asn Glu Met	Gly Trp Leu
2255	2260	2265
Asp Lys Thr Lys Ser Asp Ile	Ser Ser Leu Phe Gly	Gln Arg Ile
2270	2275	2280
Glu Val Lys Glu Asn Phe Ser	Met Gly Glu Phe Leu	Leu Asp Leu
2285	2290	2295
Arg Pro Ala Thr Ala Trp Ser	Leu Tyr Ala Val Thr	Thr Ala Val
2300	2305	2310
Leu Thr Pro Leu Leu Lys His	Leu Ile Thr Ser Asp	Tyr Ile Asn
2315	2320	2325
Thr Ser Leu Thr Ser Ile Asn	Val Gln Ala Ser Ala	Leu Phe Thr
2330	2335	2340
Leu Ala Arg Gly Phe Pro Phe	Val Asp Val Gly Val	Ser Ala Leu
2345	2350	2355
Leu Leu Ala Ala Gly Cys Trp	Gly Gln Val Thr Leu	Thr Val Thr
2360	2365	2370
Val Thr Ala Ala Thr Leu Leu	Phe Cys His Tyr Ala	Tyr Met Val
2375	2380	2385
Pro Gly Trp Gln Ala Glu Ala	Met Arg Ser Ala Gln	Arg Arg Thr
2390	2395	2400
Ala Ala Gly Ile Met Lys Asn	Ala Val Val Asp Gly	Ile Val Ala
2405	2410	2415
Thr Asp Val Pro Glu Leu Glu	Arg Thr Thr Pro Ile	Met Gln Lys
2420	2425	2430
Lys Val Gly Gln Ile Met Leu	Ile Leu Val Ser Leu	Ala Ala Val
2435	2440	2445
Val Val Asn Pro Ser Val Lys	Thr Val Arg Glu Ala	Gly Ile Leu
2450	2455	2460
Ile Thr Ala Ala Ala Val Thr	Leu Trp Glu Asn Gly	Ala Ser Ser
2465	2470	2475
Val Trp Asn Ala Thr Thr Ala	Ile Gly Leu Cys His	Ile Met Arg
2480	2485	2490
Gly Gly Trp Leu Ser Cys Leu	Ser Ile Thr Trp Thr	Leu Ile Lys
2495	2500	2505
Asn Met Glu Lys Pro Gly Leu	Lys Arg Gly Gly Ala	Lys Gly Arg
2510	2515	2520
Thr Leu Gly Glu Val Trp Lys	Glu Arg Leu Asn Gln	Met Thr Lys
2525	2530	2535
Glu Glu Phe Thr Arg Tyr Arg	Lys Glu Ala Ile Ile	Glu Val Asp
2540	2545	2550
Arg Ser Ala Ala Lys His Ala	Arg Lys Glu Gly Asn	Val Thr Gly
2555	2560	2565
Gly His Pro Val Ser Arg Gly	Thr Ala Lys Leu Arg	Trp Leu Val
2570	2575	2580
Glu Arg Arg Phe Leu Glu Pro	Val Gly Lys Val Ile	Asp Leu Gly
2585	2590	2595
Cys Gly Arg Gly Gly Trp Cys	Tyr Tyr Met Ala Thr	Gln Lys Arg
2600	2605	2610
Val Gln Glu Val Arg Gly Tyr	Thr Lys Gly Gly Pro	Gly His Glu
2615	2620	2625
Glu Pro Gln Leu Val Gln Ser	Tyr Gly Trp Asn Ile	Val Thr Met
2630	2635	2640

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Lys Ser	Gly Val Asp Val Phe	Tyr Arg Pro Ser	Glu Cys Cys Asp
2645	2650		2655
Thr Leu	Leu Cys Asp Ile Gly	Glu Ser Ser Ser	Ser Ala Glu Val
2660	2665		2670
Glu Glu	His Arg Thr Ile Arg	Val Leu Glu Met	Val Glu Asp Trp
2675	2680		2685
Leu His	Arg Gly Pro Arg Glu	Phe Cys Val Lys	Val Leu Cys Pro
2690	2695		2700
Tyr Met	Pro Lys Val Ile Glu	Lys Met Glu Leu	Leu Gln Arg Arg
2705	2710		2715
Tyr Gly	Gly Gly Leu Val Arg	Asn Pro Leu Ser	Arg Asn Ser Thr
2720	2725		2730
His Glu	Met Tyr Trp Val Ser	Arg Ala Ser Gly	Asn Val Val His
2735	2740		2745
Ser Val	Asn Met Thr Ser Gln	Val Leu Leu Gly	Arg Met Glu Lys
2750	2755		2760
Arg Thr	Trp Lys Gly Pro Gln	Tyr Glu Glu Asp	Val Asn Leu Gly
2765	2770		2775
Ser Gly	Thr Arg Ala Val Gly	Lys Pro Leu Leu	Asn Ser Asp Thr
2780	2785		2790
Ser Lys	Ile Lys Asn Arg Ile	Glu Arg Leu Arg	Arg Glu Tyr Ser
2795	2800		2805
Ser Thr	Trp His His Asp Glu	Asn His Pro Tyr	Arg Thr Trp Asn
2810	2815		2820
Tyr His	Gly Ser Tyr Asp Val	Lys Pro Thr Gly	Ser Ala Ser Ser
2825	2830		2835
Leu Val	Asn Gly Val Val Arg	Leu Leu Ser Lys	Pro Trp Asp Thr
2840	2845		2850
Ile Thr	Asn Val Thr Thr Met	Ala Met Thr Asp	Thr Thr Pro Phe
2855	2860		2865
Gly Gln	Gln Arg Val Phe Lys	Glu Lys Val Asp	Thr Lys Ala Pro
2870	2875		2880
Glu Pro	Pro Glu Gly Val Lys	Tyr Val Leu Asn	Glu Thr Thr Asn
2885	2890		2895
Trp Leu	Trp Ala Phe Leu Ala	Arg Glu Lys Arg	Pro Arg Met Cys
2900	2905		2910
Ser Arg	Glu Glu Phe Ile Arg	Lys Val Asn Ser	Asn Ala Ala Leu
2915	2920		2925
Gly Ala	Met Phe Glu Glu Gln	Asn Gln Trp Arg	Ser Ala Arg Glu
2930	2935		2940
Ala Val	Glu Asp Pro Lys Phe	Trp Glu Met Val	Asp Glu Glu Arg
2945	2950		2955
Glu Ala	His Leu Arg Gly Glu	Cys His Thr Cys	Ile Tyr Asn Met
2960	2965		2970
Met Gly	Lys Arg Glu Lys Lys	Pro Gly Glu Phe	Gly Lys Ala Lys
2975	2980		2985
Gly Ser	Arg Ala Ile Trp Phe	Met Trp Leu Gly	Ala Arg Phe Leu
2990	2995		3000
Glu Phe	Glu Ala Leu Gly Phe	Leu Asn Glu Asp	His Trp Leu Gly
3005	3010		3015
Arg Lys	Asn Ser Gly Gly Gly	Val Glu Gly Leu	Gly Leu Gln Lys
3020	3025		3030
Leu Gly	Tyr Ile Leu Arg Glu	Val Gly Thr Arg	Pro Gly Gly Lys
3035	3040		3045

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Ile Tyr	Ala Asp Asp Thr	Ala	Gly Trp Asp Thr	Arg	Ile Thr Arg
3050		3055		3060	
Ala Asp	Leu Glu Asn Glu	Ala	Lys Val Leu Glu	Leu	Leu Asp Gly
3065		3070		3075	
Glu His	Arg Arg Leu Ala	Arg	Ala Ile Ile Glu	Leu	Thr Tyr Arg
3080		3085		3090	
His Lys	Val Val Lys Val	Met	Arg Pro Ala Ala	Asp	Gly Arg Thr
3095		3100		3105	
Val Met	Asp Val Ile Ser	Arg	Glu Asp Gln Arg	Gly	Ser Gly Gln
3110		3115		3120	
Val Val	Thr Tyr Ala Leu	Asn	Thr Phe Thr Asn	Leu	Ala Val Gln
3125		3130		3135	
Leu Val	Arg Met Met Glu	Gly	Glu Gly Val Ile	Gly	Pro Asp Asp
3140		3145		3150	
Val Glu	Lys Leu Thr Lys	Gly	Lys Gly Pro Lys	Val	Arg Thr Trp
3155		3160		3165	
Leu Phe	Glu Asn Gly Glu	Glu	Arg Leu Ser Arg	Met	Ala Val Ser
3170		3175		3180	
Gly Asp	Asp Cys Val Val	Lys	Pro Leu Asp Asp	Arg	Phe Ala Thr
3185		3190		3195	
Ser Leu	His Phe Leu Asn	Ala	Met Ser Lys Val	Arg	Lys Asp Ile
3200		3205		3210	
Gln Glu	Trp Lys Pro Ser	Thr	Gly Trp Tyr Asp	Trp	Gln Gln Val
3215		3220		3225	
Pro Phe	Cys Ser Asn His	Phe	Thr Glu Leu Ile	Met	Lys Asp Gly
3230		3235		3240	
Arg Thr	Leu Val Val Pro	Cys	Arg Gly Gln Asp	Glu	Leu Val Gly
3245		3250		3255	
Arg Ala	Arg Ile Ser Pro	Gly	Ala Gly Trp Asn	Val	Arg Asp Thr
3260		3265		3270	
Ala Cys	Leu Ala Lys Ser	Tyr	Ala Gln Met Trp	Leu	Leu Leu Tyr
3275		3280		3285	
Phe His	Arg Arg Asp Leu	Arg	Leu Met Ala Asn	Ala	Ile Cys Ser
3290		3295		3300	
Ala Val	Pro Val Asn Trp	Val	Pro Thr Gly Arg	Thr	Thr Trp Ser
3305		3310		3315	
Ile His	Ala Gly Gly Glu	Trp	Met Thr Thr Glu	Asp	Met Leu Glu
3320		3325		3330	
Val Trp	Asn Arg Val Trp	Ile	Glu Glu Asn Glu	Trp	Met Glu Asp
3335		3340		3345	
Lys Thr	Pro Val Glu Lys	Trp	Ser Asp Val Pro	Tyr	Ser Gly Lys
3350		3355		3360	
Arg Glu	Asp Ile Trp Cys	Gly	Ser Leu Ile Gly	Thr	Arg Ala Arg
3365		3370		3375	
Ala Thr	Trp Ala Glu Asn	Ile	Gln Val Ala Ile	Asn	Gln Val Arg
3380		3385		3390	
Ala Ile	Ile Gly Asp Glu	Lys	Tyr Val Asp Tyr	Met	Ser Ser Leu
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Lys Arg	Tyr Glu Asp Thr	Thr	Leu Val Glu Asp	Thr	Val Leu
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 <211> LENGTH: 10996
 <212> TYPE: DNA

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<223> OTHER INFORMATION: Recombinant West Nile virus/Dengue-1 virus
      chimera
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (97)..(10362)

<400> SEQUENCE: 3

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                        Met Ser Lys Lys Pro Gly
                        1          5

ggg ccc ggc aag agc cgg gct gtc aat atg cta aaa cgc gga atg ccc      162
Gly Pro Gly Lys Ser Arg Ala Val Asn Met Leu Lys Arg Gly Met Pro
          10          15          20

cgc gtg ttg tcc ttg att gga ctg aag agg gct atg ttg agc ctg atc      210
Arg Val Leu Ser Leu Ile Gly Leu Lys Arg Ala Met Leu Ser Leu Ile
          25          30          35

gac ggc aag ggg cca ata cga ttt gtg ttg gct ctc ttg gcg ttc ttc      258
Asp Gly Lys Gly Pro Ile Arg Phe Val Leu Ala Leu Leu Ala Phe Phe
          40          45          50

agg ttc aca gca att gct ccg acc cga gca gtg ctg gat cga tgg aga      306
Arg Phe Thr Ala Ile Ala Pro Thr Arg Ala Val Leu Asp Arg Trp Arg
          55          60          65          70

ggg gtg aac aaa caa aca gcg atg aaa cac ctt ctg agt ttt aag aag      354
Gly Val Asn Lys Gln Thr Ala Met Lys His Leu Leu Ser Phe Lys Lys
          75          80          85

gaa cta ggg acc ttg acc agt gct atc aat cgg cgg agc tca aaa caa      402
Glu Leu Gly Thr Leu Thr Ser Ala Ile Asn Arg Arg Ser Ser Lys Gln
          90          95          100

aag aaa aga tcc gtg acc atg ctc ctt atg ctg ctg ccc aca gcc ctg      450
Lys Lys Arg Ser Val Thr Met Lys Leu Met Leu Leu Pro Thr Ala Leu
          105          110          115

gcg ttc cat ctg acg aca cga ggg gga gag ccg cat atg ata gtt agc      498
Ala Phe His Leu Thr Thr Arg Gly Gly Glu Pro His Met Ile Val Ser
          120          125          130

aag cag gaa aga gga aag tca ctt ttg ttc aag acc tct gca ggt gtc      546
Lys Gln Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ser Ala Gly Val
          135          140          145          150

aac atg tgc acc ctc att gcg atg gat ttg gga gag ttg tgt gag gac      594
Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Leu Cys Glu Asp
          155          160          165

acg atg acc tac aaa tgc ccc cgg atc act gag gcg gaa cca gat gac      642
Thr Met Thr Tyr Lys Cys Pro Arg Ile Thr Glu Ala Glu Pro Asp Asp
          170          175          180

gtt gac tgt tgg tgc aat gcc acg gac aca tgg gtg acc tat gga acg      690
Val Asp Cys Trp Cys Asn Ala Thr Asp Thr Trp Val Thr Tyr Gly Thr
          185          190          195

tgc tct caa act ggc gaa cac cga cga gac aaa cgt tcc gtc gca ttg      738
Cys Ser Gln Thr Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala Leu
          200          205          210

gcc cca cac gtg ggg ctt ggc cta gaa aca aga gcc gaa acg tgg atg      786
Ala Pro His Val Gly Leu Gly Leu Glu Thr Arg Ala Glu Thr Trp Met
          215          220          225          230

tcc tct gaa ggt gct tgg aaa cag ata caa aaa gta gag act tgg gct      834
Ser Ser Glu Gly Ala Trp Lys Gln Ile Gln Lys Val Glu Thr Trp Ala
          235          240          245

ctg aga cat cca gga ttc acg gtg ata gcc ctt ttt cta gca cat gcc      882
Leu Arg His Pro Gly Phe Thr Val Ile Ala Leu Phe Leu Ala His Ala
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ata gga aca tcc atc acc cag aaa ggg atc att ttc att ttg ctg atg Ile Gly Thr Ser Ile Thr Gln Lys Gly Ile Ile Phe Ile Leu Leu Met 265 270 275	930
ctg gta aca cca tct atg gcc atg cga tgc gtg gga ata ggc aac aga Leu Val Thr Pro Ser Met Ala Met Arg Cys Val Gly Ile Gly Asn Arg 280 285 290	978
gac ttc gtg gaa gga ctg tca gga gca aca tgg gtg gat gtg gta ctg Asp Phe Val Glu Gly Leu Ser Gly Ala Thr Trp Val Asp Val Val Leu 295 300 305 310	1026
gag cat gga agt tgc gtc acc acc atg gca aaa aac aaa cca aca ctg Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr Leu 315 320 325	1074
gac att gaa ctc ttg aag acg gag gtc aca aac cct gca gtt ctg cgt Asp Ile Glu Leu Leu Lys Thr Glu Val Thr Asn Pro Ala Val Leu Arg 330 335 340	1122
aaa ttg tgc att gaa gct aaa ata tca aac acc acc acc gat tgc aga Lys Leu Cys Ile Glu Ala Lys Ile Ser Asn Thr Thr Thr Asp Ser Arg 345 350 355	1170
tgt cca aca caa gga gaa gcc aca ctg gtg gaa gaa caa gac gcg aac Cys Pro Thr Gln Gly Glu Ala Thr Leu Val Glu Glu Gln Asp Ala Asn 360 365 370	1218
ttt gtg tgc cga cga acg ttc gtg gac aga ggc tgg ggc aat ggc tgt Phe Val Cys Arg Arg Thr Phe Val Asp Arg Gly Trp Gly Asn Gly Cys 375 380 385 390	1266
ggg cta ttc gga aaa ggt agt cta ata acg tgt gcc aag ttt aag tgt Gly Leu Phe Gly Lys Gly Ser Leu Ile Thr Cys Ala Lys Phe Lys Cys 395 400 405	1314
gtg aca aaa cta gaa gga aag ata gtt caa tat gaa aac cta aaa tat Val Thr Lys Leu Glu Gly Lys Ile Val Gln Tyr Glu Asn Leu Lys Tyr 410 415 420	1362
tca gtg ata gtc acc gtc cac act gga gat cag cac cag gtg gga aat Ser Val Ile Val Thr Val His Thr Gly Asp Gln His Gln Val Gly Asn 425 430 435	1410
gag act aca gaa cat gga aca act gca acc ata aca cct caa gct cct Glu Thr Thr Glu His Gly Thr Thr Ala Thr Ile Thr Pro Gln Ala Pro 440 445 450	1458
acg tgc gaa ata cag ctg acc gac tac gga acc ctt aca tta gat tgt Thr Ser Glu Ile Gln Leu Thr Asp Tyr Gly Thr Leu Thr Leu Asp Cys 455 460 465 470	1506
tca cct agg aca ggg cta gat ttt aac gag atg gtg ttg ctg aca atg Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Thr Met 475 480 485	1554
aaa gaa aga tca tgg ctt gtc cac aaa caa tgg ttt cca gac tta cca Lys Glu Arg Ser Trp Leu Val His Lys Gln Trp Phe Pro Asp Leu Pro 490 495 500	1602
ctg cct tgg acc tct ggg gct tca aca tcc caa gag act tgg aac aga Leu Pro Trp Thr Ser Gly Ala Ser Thr Ser Gln Glu Thr Trp Asn Arg 505 510 515	1650
caa gat tta ctg gtc aca ttt aag aca gct cat gca aag aag cag gaa Gln Asp Leu Leu Val Thr Phe Lys Thr Ala His Ala Lys Lys Gln Glu 520 525 530	1698
gta gtc gta cta gga tca caa gaa gga gca atg cac act gcg ctg act Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu Thr 535 540 545 550	1746
gga gcg aca gaa atc caa acg tca gga acg aca aca att ttc gca gga Gly Ala Thr Glu Ile Gln Thr Ser Gly Thr Thr Thr Ile Phe Ala Gly 555 560 565	1794
cac cta aaa tgc aga cta aaa atg gac aaa cta act tta aaa ggg atg His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Thr Leu Lys Gly Met 570 575 580	1842

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tca tat gtg atg tgc aca ggc tca ttc aag tta gag aaa gaa gtg gct Ser Tyr Val Met Cys Thr Gly Ser Phe Lys Leu Glu Lys Glu Val Ala 585 590 595	1890
gag acc cag cat gga act gtt ctg gtg cag gtt aaa tat gaa gga aca Glu Thr Gln His Gly Thr Val Leu Val Gln Val Lys Tyr Glu Gly Thr 600 605 610	1938
gac gca cca tgc aag att ccc ttt tgc acc caa gat gag aaa gga gca Asp Ala Pro Cys Lys Ile Pro Phe Ser Thr Gln Asp Glu Lys Gly Ala 615 620 625 630	1986
acc cag aat ggg aga tta ata aca gcc aac ccc ata gtc act gac aaa Thr Gln Asn Gly Arg Leu Ile Thr Ala Asn Pro Ile Val Thr Asp Lys 635 640 645	2034
gaa aaa cca gtc aat att gag gca gaa cca ccc ttt ggt gag agc tac Glu Lys Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Glu Ser Tyr 650 655 660	2082
atc gtg gta gga gca ggt gaa aaa gct ttg aaa cta agc tgg ttc aag Ile Val Val Gly Ala Gly Glu Lys Ala Leu Lys Leu Ser Trp Phe Lys 665 670 675	2130
aaa gga agc agc ata ggg aaa atg ttt gaa gca act gcc cga gga gca Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly Ala 680 685 690	2178
cga agg atg gcc att ctg gga gac acc gca tgg gac ttc ggt tct ata Arg Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser Ile 695 700 705 710	2226
gga gga gtg ttc acg tct atg gga aaa ctg gta cac cag gtt ttt gga Gly Gly Val Phe Thr Ser Met Gly Lys Leu Val His Gln Val Phe Gly 715 720 725	2274
act gca tat gga gtt ttg ttt agc gga gtt tct tgg acc atg aaa ata Thr Ala Tyr Gly Val Leu Phe Ser Gly Val Ser Trp Thr Met Lys Ile 730 735 740	2322
gga ata ggg att ctg ctg aca tgg cta gga tta aat tca agg aac acg Gly Ile Gly Ile Leu Leu Thr Trp Leu Gly Leu Asn Ser Arg Asn Thr 745 750 755	2370
tcc ctt tgc atg atg tgc atc gca gtt ggc atg gtc aca ctg tac cta Ser Leu Ser Met Met Cys Ile Ala Val Gly Met Val Thr Leu Tyr Leu 760 765 770	2418
gga gtc atg gtt cag gca gat tcc gga tgt gcc ata gac atc agc cgg Gly Val Met Val Gln Ala Asp Ser Gly Cys Ala Ile Asp Ile Ser Arg 775 780 785 790	2466
caa gag ctg aga tgt gga agt gga gtg ttc ata cac aat gat gtg gag Gln Glu Leu Arg Cys Gly Ser Gly Val Phe Ile His Asn Asp Val Glu 795 800 805	2514
gct tgg atg gac cgg tac aag tat tac cct gaa acg cca caa ggc cta Ala Trp Met Asp Arg Tyr Lys Tyr Tyr Pro Glu Thr Pro Gln Gly Leu 810 815 820	2562
gcc aag atc att cag aaa gct cat aag gaa gga gtg tgc ggt cta cga Ala Lys Ile Ile Gln Lys Ala His Lys Glu Gly Val Cys Gly Leu Arg 825 830 835	2610
tca gtt tcc aga ctg gag cat caa atg tgg gaa gca gtg aag gac gag Ser Val Ser Arg Leu Glu His Gln Met Trp Glu Ala Val Lys Asp Glu 840 845 850	2658
ctg aac act ctt ttg aag gag aat ggt gtg gac ctt agt gtc gtg gtt Leu Asn Thr Leu Leu Lys Glu Asn Gly Val Asp Leu Ser Val Val Val 855 860 865 870	2706
gag aaa cag gag gga atg tac aag tca gca cct aaa cgc ctc acc gcc Glu Lys Gln Glu Gly Met Tyr Lys Ser Ala Pro Lys Arg Leu Thr Ala 875 880 885	2754
acc acg gaa aaa ttg gaa att ggc tgg aag gcc tgg gga aag agt att Thr Thr Glu Lys Leu Glu Ile Gly Trp Lys Ala Trp Gly Lys Ser Ile 890 895 900	2802

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tta ttt gca cca gaa ctc gcc aac aac acc ttt gtg gtt gat ggt ccg Leu Phe Ala Pro Glu Leu Ala Asn Asn Thr Phe Val Val Asp Gly Pro 905 910 915	2850
gag acc aag gaa tgt ccg act cag aat cgc gct tgg aat agc tta gaa Glu Thr Lys Glu Cys Pro Thr Gln Asn Arg Ala Trp Asn Ser Leu Glu 920 925 930	2898
gtg gag gat ttt gga ttt ggt ctc acc agc act cgg atg ttc ctg aag Val Glu Asp Phe Gly Phe Gly Leu Thr Ser Thr Arg Met Phe Leu Lys 935 940 945 950	2946
gtc aga gag agc aac aca act gaa tgt gac tcg aag atc att gga acg Val Arg Glu Ser Asn Thr Thr Glu Cys Asp Ser Lys Ile Ile Gly Thr 955 960 965	2994
gct gtc aag aac aac ttg gcg atc cac agt gac ctg tcc tat tgg att Ala Val Lys Asn Asn Leu Ala Ile His Ser Asp Leu Ser Tyr Trp Ile 970 975 980	3042
gaa agc agg ctc aat gat acg tgg aag ctt gaa agg gca gtt ctg ggt Glu Ser Arg Leu Asn Asp Thr Trp Lys Leu Glu Arg Ala Val Leu Gly 985 990 995	3090
gaa gtc aaa tca tgt acg tgg cct gag acg cat acc ttg tgg ggc Glu Val Lys Ser Cys Thr Trp Pro Glu Thr His Thr Leu Trp Gly 1000 1005 1010	3135
gat gga atc ctt gag agt gac ttg ata ata cca gtc aca ctg gcg Asp Gly Ile Leu Glu Ser Asp Leu Ile Ile Pro Val Thr Leu Ala 1015 1020 1025	3180
gga cca cga agc aat cac aat cgg aga cct ggg tac aag aca caa Gly Pro Arg Ser Asn His Asn Arg Arg Pro Gly Tyr Lys Thr Gln 1030 1035 1040	3225
aac cag ggc cca tgg gac gaa ggc cgg gta gag att gac ttc gat Asn Gln Gly Pro Trp Asp Glu Gly Arg Val Glu Ile Asp Phe Asp 1045 1050 1055	3270
tac tgc cca gga act acg gtc acc ctg agt gag agc tgc gga cac Tyr Cys Pro Gly Thr Thr Val Thr Leu Ser Glu Ser Cys Gly His 1060 1065 1070	3315
cgt gga cct gcc act cgc acc acc aca gag agc gga aag ttg ata Arg Gly Pro Ala Thr Arg Thr Thr Thr Glu Ser Gly Lys Leu Ile 1075 1080 1085	3360
aca gat tgg tgc tgc agg agc tgc acc tta cca cca ctg cgc tac Thr Asp Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr 1090 1095 1100	3405
caa act gac agc ggc tgt tgg tat ggt atg gag atc aga cca cag Gln Thr Asp Ser Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Gln 1105 1110 1115	3450
aga cat gat gaa aag acc ctc gtg cag tca caa gtg aat gct tat Arg His Asp Glu Lys Thr Leu Val Gln Ser Gln Val Asn Ala Tyr 1120 1125 1130	3495
aat gct gat atg att gac cct ttt cag ttg ggc ctt ctg gtc gtg Asn Ala Asp Met Ile Asp Pro Phe Gln Leu Gly Leu Leu Val Val 1135 1140 1145	3540
ttc ttg gcc acc cag gag gtc ctt cgc aag agg tgg aca gcc aag Phe Leu Ala Thr Gln Glu Val Leu Arg Lys Arg Trp Thr Ala Lys 1150 1155 1160	3585
atc agc atg cca gct ata ctg att gct ctg cta gtc ctg gtg ttt Ile Ser Met Pro Ala Ile Leu Ile Ala Leu Leu Val Leu Val Phe 1165 1170 1175	3630
ggg ggc att act tac act gat gtg tta cgc tat gtc atc ttg gtg Gly Gly Ile Thr Tyr Thr Asp Val Leu Arg Tyr Val Ile Leu Val 1180 1185 1190	3675
ggg gca gct ttc gca gaa tct aat tcg gga gga gac gtg gta cac Gly Ala Ala Phe Ala Glu Ser Asn Ser Gly Gly Asp Val Val His 1195 1200 1205	3720

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ttg gcg	ctc atg gcg acc	ttc aag ata caa cca	gtg ttt atg gtg	3765
Leu Ala	Leu Met Ala Thr	Phe Lys Ile Gln Pro	Val Phe Met Val	
1210		1215	1220	
gca tcg	ttt ctc aaa gcg aga	tgg acc aac cag gag	aac att ttg	3810
Ala Ser	Phe Leu Lys Ala	Arg Trp Thr Asn Gln	Glu Asn Ile Leu	
1225		1230	1235	
ttg atg	ttg gcg gct gtt	ttc ttt caa atg gct	tat tac gat gcc	3855
Leu Met	Leu Ala Ala Val	Phe Phe Gln Met Ala	Tyr Tyr Asp Ala	
1240		1245	1250	
cgc caa	att ctg ctc tgg gag	atc cct gat gtg ttg	aat tca ctg	3900
Arg Gln	Ile Leu Leu Trp	Glu Ile Pro Asp Val	Leu Asn Ser Leu	
1255		1260	1265	
gcg gta	gct tgg atg ata ctg	aga gcc ata aca ttc	aca acg aca	3945
Ala Val	Ala Trp Met Ile	Leu Arg Ala Ile Thr	Phe Thr Thr Thr	
1270		1275	1280	
tca aac	gtg gtt gtt ccg ctg	cta gcc ctg cta aca	ccc ggg ctg	3990
Ser Asn	Val Val Val Pro	Leu Leu Ala Leu Leu	Thr Pro Gly Leu	
1285		1290	1295	
aga tgc	ttg aat ctg gat gtg	tac agg ata ctg ctg	ttg atg gtc	4035
Arg Cys	Leu Asn Leu Asp	Val Tyr Arg Ile Leu	Leu Leu Met Val	
1300		1305	1310	
gga ata	ggc agc ttg atc agg	gag aag agg agt gca	gct gca aaa	4080
Gly Ile	Gly Ser Leu Ile	Arg Glu Lys Arg Ser	Ala Ala Ala Lys	
1315		1320	1325	
aag aaa	gga gca agt ctg cta	tgc ttg gct cta gcc	tca aca gga	4125
Lys Lys	Gly Ala Ser Leu	Leu Cys Leu Ala Leu	Ala Ser Thr Gly	
1330		1335	1340	
ctt ttc	aac ccc atg atc ctt	gct gct gga ctg att	gca tgt gat	4170
Leu Phe	Asn Pro Met Ile	Leu Ala Ala Gly Leu	Ile Ala Cys Asp	
1345		1350	1355	
ccc aac	cgt aaa cgc gga tgg	ccc gca act gaa gtg	atg aca gct	4215
Pro Asn	Arg Lys Arg Gly	Trp Pro Ala Thr Glu	Val Met Thr Ala	
1360		1365	1370	
gtc ggc	cta atg ttt gcc atc	gtc gga ggg ctg gca	gag ctt gac	4260
Val Gly	Leu Met Phe Ala	Ile Val Gly Gly Leu	Ala Glu Leu Asp	
1375		1380	1385	
att gac	tcc atg gcc att cca	atg act atc gcg ggg	ctc atg ttt	4305
Ile Asp	Ser Met Ala Ile	Pro Met Thr Ile Ala	Gly Leu Met Phe	
1390		1395	1400	
gct gct	ttc gtg att tct ggg	aaa tca aca gat atg	ttg att gag	4350
Ala Ala	Phe Val Ile Ser	Gly Lys Ser Thr Asp	Met Trp Ile Glu	
1405		1410	1415	
aga acg	gcg gac att tcc tgg	gaa agt gat gca gaa	att aca ggc	4395
Arg Thr	Ala Asp Ile Ser	Trp Glu Ser Asp Ala	Glu Ile Thr Gly	
1420		1425	1430	
tcg agc	gaa aga gtt gat gtg	cgg ctt gat gat gat	gga aac ttc	4440
Ser Ser	Glu Arg Val Asp	Val Arg Leu Asp Asp	Asp Gly Asn Phe	
1435		1440	1445	
cag ctc	atg aat gat cca gga	gca cct tgg aag ata	ttg atg ctc	4485
Gln Leu	Met Asn Asp Pro	Gly Ala Pro Trp Lys	Ile Trp Met Leu	
1450		1455	1460	
aga atg	gtc tgt ctc gcg att	agt gcg tac acc ccc	ttg gca atc	4530
Arg Met	Val Cys Leu Ala	Ile Ser Ala Tyr Thr	Pro Trp Ala Ile	
1465		1470	1475	
ttg ccc	tca gta gtt gga ttt	tgg ata act ctc caa	tac aca aag	4575
Leu Pro	Ser Val Val Gly	Phe Trp Ile Thr Leu	Gln Tyr Thr Lys	
1480		1485	1490	
aga gga	ggc gtg ttg tgg gac	act ccc tca cca aag	gag tac aaa	4620
Arg Gly	Gly Val Leu Trp	Asp Thr Pro Ser Pro	Lys Glu Tyr Lys	
1495		1500	1505	

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aag ggg	gac acg acc acc ggc	gtc tac agg atc atg	act cgt ggg	4665
Lys Gly	Asp Thr Thr Thr Gly	Val Tyr Arg Ile Met	Thr Arg Gly	
1510	1515	1520		
ctg ctc	ggc agt tat caa gca	gga gcg ggc gtg atg	gtt gaa ggt	4710
Leu Leu	Gly Ser Tyr Gln Ala	Gly Ala Gly Val Met	Val Glu Gly	
1525	1530	1535		
gtt ttc	cac acc ctt tgg cat	aca aca aaa gga gcc	gct ttg atg	4755
Val Phe	His Thr Leu Trp His	Thr Thr Lys Gly Ala	Ala Leu Met	
1540	1545	1550		
agc gga	gag ggc cgc ctg gac	cca tac tgg ggc agt	gtc aag gag	4800
Ser Gly	Glu Gly Arg Leu Asp	Pro Tyr Trp Gly Ser	Val Lys Glu	
1555	1560	1565		
gat cga	ctt tgt tac gga gga	ccc tgg aaa ttg cag	cac aag tgg	4845
Asp Arg	Leu Cys Tyr Gly Gly	Pro Trp Lys Leu Gln	His Lys Trp	
1570	1575	1580		
aac ggg	cag gat gag gtg cag	atg att gtg gtg gaa	cct ggc agg	4890
Asn Gly	Gln Asp Glu Val Gln	Met Ile Val Val Glu	Pro Gly Arg	
1585	1590	1595		
aac gtt	aag aac gtc cag acg	aaa cca ggg gtg ttc	aaa aca cct	4935
Asn Val	Lys Asn Val Gln Thr	Lys Pro Gly Val Phe	Lys Thr Pro	
1600	1605	1610		
gaa gga	gaa atc ggg gcc gtg	act ttg gac ttc ccc	act gga aca	4980
Glu Gly	Glu Ile Gly Ala Val	Thr Leu Asp Phe Pro	Thr Gly Thr	
1615	1620	1625		
tca ggc	tca cca ata gtg gac	aaa aac ggt gat gtg	att ggg ctt	5025
Ser Gly	Ser Pro Ile Val Asp	Lys Asn Gly Asp Val	Ile Gly Leu	
1630	1635	1640		
tat ggc	aat gga gtc ata atg	ccc aac ggc tca tac	ata agc gcg	5070
Tyr Gly	Asn Gly Val Ile Met	Pro Asn Gly Ser Tyr	Ile Ser Ala	
1645	1650	1655		
ata gtg	cag ggt gaa agg atg	gat gag cca atc cca	gcc gga ttc	5115
Ile Val	Gln Gly Glu Arg Met	Asp Glu Pro Ile Pro	Ala Gly Phe	
1660	1665	1670		
gaa cct	gag atg ctg agg aaa	aaa cag atc act gta	ctg gat ctc	5160
Glu Pro	Glu Met Leu Arg Lys	Lys Gln Ile Thr Val	Leu Asp Leu	
1675	1680	1685		
cat ccc	ggc gcc ggt aaa aca	agg agg att ctg cca	cag atc atc	5205
His Pro	Gly Ala Gly Lys Thr	Arg Arg Ile Leu Pro	Gln Ile Ile	
1690	1695	1700		
aaa gag	gcc ata aac aga aga	ctg aga aca gcc gtg	cta gca cca	5250
Lys Glu	Ala Ile Asn Arg Arg	Leu Arg Thr Ala Val	Leu Ala Pro	
1705	1710	1715		
acc agg	gtt gtg gct gct gag	atg gct gaa gca ctg	aga gga ctg	5295
Thr Arg	Val Val Ala Ala Glu	Met Ala Glu Ala Leu	Arg Gly Leu	
1720	1725	1730		
ccc atc	cgg tac cag aca tcc	gca gtg ccc aga gaa	cat aat gga	5340
Pro Ile	Arg Tyr Gln Thr Ser	Ala Val Pro Arg Glu	His Asn Gly	
1735	1740	1745		
aat gag	att gtt gat gtc atg	tgt cat gct acc ctc	acc cac agg	5385
Asn Glu	Ile Val Asp Val Met	Cys His Ala Thr Leu	Thr His Arg	
1750	1755	1760		
ctg atg	tct cct cac agg gtg	ccg aac tac aac ctg	ttc gtg atg	5430
Leu Met	Ser Pro His Arg Val	Pro Asn Tyr Asn Leu	Phe Val Met	
1765	1770	1775		
gat gag	gct cat ttc acc gac	cca gct agc att gca	gca aga ggt	5475
Asp Glu	Ala His Phe Thr Asp	Pro Ala Ser Ile Ala	Ala Arg Gly	
1780	1785	1790		
tac att	tcc aca aag gtc gag	cta ggg gag gcg gcg	gca ata ttc	5520
Tyr Ile	Ser Thr Lys Val Glu	Leu Gly Glu Ala Ala	Ala Ile Phe	
1795	1800	1805		

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atg aca gcc acc cca cca ggc act tca gat cca ttc cca gag tcc	5565
Met Thr Ala Thr Pro Pro Gly Thr Ser Asp Pro Phe Pro Glu Ser	
1810 1815 1820	
aat tca cca att tcc gac tta cag act gag atc ccg gat cga gct	5610
Asn Ser Pro Ile Ser Asp Leu Gln Thr Glu Ile Pro Asp Arg Ala	
1825 1830 1835	
tgg aac tct gga tac gaa tgg atc aca gaa tac acc ggg aag acg	5655
Trp Asn Ser Gly Tyr Glu Trp Ile Thr Glu Tyr Thr Gly Lys Thr	
1840 1845 1850	
gtt tgg ttt gtg cct agt gtc aag atg ggg aat gag att gcc ctt	5700
Val Trp Phe Val Pro Ser Val Lys Met Gly Asn Glu Ile Ala Leu	
1855 1860 1865	
tgc cta caa cgt gct gga aag aaa gta gtc caa ttg aac aga aag	5745
Cys Leu Gln Arg Ala Gly Lys Lys Val Val Gln Leu Asn Arg Lys	
1870 1875 1880	
tcg tac gag acg gag tac cca aaa tgt aag aac gat gat tgg gac	5790
Ser Tyr Glu Thr Glu Tyr Pro Lys Cys Lys Asn Asp Asp Trp Asp	
1885 1890 1895	
ttt gtt atc aca aca gac ata tct gaa atg ggg gct aac ttc aag	5835
Phe Val Ile Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys	
1900 1905 1910	
gcg agc agg gtg att gac agc cgg aag agt gtg aaa cca acc atc	5880
Ala Ser Arg Val Ile Asp Ser Arg Lys Ser Val Lys Pro Thr Ile	
1915 1920 1925	
ata aca gaa gga gaa ggg aga gtg atc ctg gga gaa cca tct gca	5925
Ile Thr Glu Gly Glu Gly Arg Val Ile Leu Gly Glu Pro Ser Ala	
1930 1935 1940	
gtg aca gca gct agt gcc gcc cag aga cgt gga cgt atc ggt aga	5970
Val Thr Ala Ala Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg	
1945 1950 1955	
aat ccg tcg caa gtt ggt gat gag tac tgt tat ggg ggg cac acg	6015
Asn Pro Ser Gln Val Gly Asp Glu Tyr Cys Tyr Gly Gly His Thr	
1960 1965 1970	
aat gaa gac gac tcg aac ttc gcc cat tgg act gag gca cga atc	6060
Asn Glu Asp Asp Ser Asn Phe Ala His Trp Thr Glu Ala Arg Ile	
1975 1980 1985	
atg ctg gac aac atc aac atg cca aac gga ctg atc gct caa ttc	6105
Met Leu Asp Asn Ile Asn Met Pro Asn Gly Leu Ile Ala Gln Phe	
1990 1995 2000	
tac caa cca gag cgt gag aag gta tat acc atg gat ggg gaa tac	6150
Tyr Gln Pro Glu Arg Glu Lys Val Tyr Thr Met Asp Gly Glu Tyr	
2005 2010 2015	
cgg ctc aga gga gaa gag aga aaa aac ttt ctg gaa ctg ttg agg	6195
Arg Leu Arg Gly Glu Glu Arg Lys Asn Phe Leu Glu Leu Leu Arg	
2020 2025 2030	
act gca gat ctg cca gtt tgg ctg gct tac aag gtt gca gcg gct	6240
Thr Ala Asp Leu Pro Val Trp Leu Ala Tyr Lys Val Ala Ala Ala	
2035 2040 2045	
gga gtg tca tac cac gac cgg agg tgg tgc ttt gat ggt cct agg	6285
Gly Val Ser Tyr His Asp Arg Arg Trp Cys Phe Asp Gly Pro Arg	
2050 2055 2060	
aca aac aca att tta gaa gac aac aac gaa gtg gaa gtc atc acg	6330
Thr Asn Thr Ile Leu Glu Asp Asn Asn Glu Val Glu Val Ile Thr	
2065 2070 2075	
aag ctt ggt gaa agg aag att ctg agg ccg cgc tgg att gac gcc	6375
Lys Leu Gly Glu Arg Lys Ile Leu Arg Pro Arg Trp Ile Asp Ala	
2080 2085 2090	
agg gtg tac tcg gat cac cag gca cta aag gcg ttc aag gac ttc	6420
Arg Val Tyr Ser Asp His Gln Ala Leu Lys Ala Phe Lys Asp Phe	
2095 2100 2105	

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gcc tcg gga aaa cgt tct cag ata ggg ctc att gag gtt ctg gga 6465 Ala Ser Gly Lys Arg Ser Gln Ile Gly Leu Ile Glu Val Leu Gly 2110 2115 2120
aag atg cct gag cac ttc atg ggg aag aca tgg gaa gca ctt gac 6510 Lys Met Pro Glu His Phe Met Gly Lys Thr Trp Glu Ala Leu Asp 2125 2130 2135
acc atg tac gtt gtg gcc act gca gag aaa gga gga aga gct cac 6555 Thr Met Tyr Val Val Ala Thr Ala Glu Lys Gly Gly Arg Ala His 2140 2145 2150
aga atg gcc ctg gag gaa ctg cca gat gct ctt cag aca att gcc 6600 Arg Met Ala Leu Glu Glu Leu Pro Asp Ala Leu Gln Thr Ile Ala 2155 2160 2165
ttg att gcc tta ttg agt gtg atg acc atg gga gta ttc ttc ctc 6645 Leu Ile Ala Leu Leu Ser Val Met Thr Met Gly Val Phe Phe Leu 2170 2175 2180
ctc atg cag cgg aag ggc att gga aag ata ggt ttg gga ggc gct 6690 Leu Met Gln Arg Lys Gly Ile Gly Lys Ile Gly Leu Gly Gly Ala 2185 2190 2195
gtc ttg gga gtc gcg acc ttt ttc tgt tgg atg gct gaa gtt cca 6735 Val Leu Gly Val Ala Thr Phe Phe Cys Trp Met Ala Glu Val Pro 2200 2205 2210
gga acg aag atc gcc gga atg ttg ctg ctc tcc ctt ctc ttg atg 6780 Gly Thr Lys Ile Ala Gly Met Leu Leu Leu Ser Leu Leu Leu Met 2215 2220 2225
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gat gag Asp Glu 2815	aac cac cca tat aga Asn His Pro Tyr Arg 2820	acc tgg aac tat cac Thr Trp Asn Tyr His 2825	ggc agt tat Gly Ser Tyr 2830	8580
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Thr Ala	Gly Trp Asp Thr	Arg	Ile Thr Arg Ala	Asp	Leu Glu Asn	
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Glu Ala	Lys Val Leu Glu	Leu	Leu Asp Gly Glu	His	Arg Arg Leu	
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Ala Arg	Ala Ile Ile Glu	Leu	Thr Tyr Arg His	Lys	Val Val Lys	
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Val Met	Arg Pro Ala Ala	Asp	Gly Arg Thr Val	Met	Asp Val Ile	
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Ser Arg	Glu Asp Gln Arg	Gly	Ser Gly Gln Val	Val	Thr Tyr Ala	
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Glu Gly	Glu Gly Val Ile	Gly	Pro Asp Asp Val	Glu	Lys Leu Thr	
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Lys Gly	Lys Gly Pro Lys	Val	Arg Thr Trp Leu	Phe	Glu Asn Gly	
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Glu Glu	Arg Leu Ser Arg	Met	Ala Val Ser Gly	Asp	Asp Cys Val	
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Val Lys	Pro Leu Asp Asp	Arg	Phe Ala Thr Ser	Leu	His Phe Leu	
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Asn Ala	Met Ser Lys Val	Arg	Lys Asp Ile Gln	Glu	Trp Lys Pro	
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Ser Thr	Gly Trp Tyr Asp	Trp	Gln Gln Val Pro	Phe	Cys Ser Asn	
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His Phe	Thr Glu Leu Ile	Met	Lys Asp Gly Arg	Thr	Leu Val Val	
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Pro Cys	Arg Gly Gln Asp	Glu	Leu Val Gly Arg	Ala	Arg Ile Ser	
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Pro Gly	Ala Gly Trp Asn	Val	Arg Asp Thr Ala	Cys	Leu Ala Lys	
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Ser Tyr	Ala Gln Met Trp	Leu	Leu Leu Tyr Phe	His	Arg Arg Asp	
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Lys Trp	Ser Asp Val Pro Tyr	Ser Gly Lys Arg Glu	Asp Ile Trp			
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Cys Gly	Ser Leu Ile Gly Thr	Arg Ala Arg Ala Thr	Trp Ala Glu			
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Glu Lys	Tyr Val Asp Tyr Met	Ser Ser Leu Lys Arg	Tyr Glu Asp			
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Leu Leu Ser Phe Lys Lys Glu Leu Gly Thr Leu Thr Ser Ala Ile Asn	

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Pro	Phe	Gly	Glu	Ser	Tyr	Ile	Val	Val	Gly	Ala	Gly	Glu	Lys	Ala	Leu
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			740					745					750		
Leu	Asn	Ser	Arg	Asn	Thr	Ser	Leu	Ser	Met	Met	Cys	Ile	Ala	Val	Gly
		755					760					765			
Met	Val	Thr	Leu	Tyr	Leu	Gly	Val	Met	Val	Gln	Ala	Asp	Ser	Gly	Cys
						775					780				
Ala	Ile	Asp	Ile	Ser	Arg	Gln	Glu	Leu	Arg	Cys	Gly	Ser	Gly	Val	Phe
785					790					795					800
Ile	His	Asn	Asp	Val	Glu	Ala	Trp	Met	Asp	Arg	Tyr	Lys	Tyr	Tyr	Pro
			805						810					815	
Glu	Thr	Pro	Gln	Gly	Leu	Ala	Lys	Ile	Ile	Gln	Lys	Ala	His	Lys	Glu
			820					825					830		
Gly	Val	Cys	Gly	Leu	Arg	Ser	Val	Ser	Arg	Leu	Glu	His	Gln	Met	Trp
		835					840					845			
Glu	Ala	Val	Lys	Asp	Glu	Leu	Asn	Thr	Leu	Leu	Lys	Glu	Asn	Gly	Val
		850				855					860				
Asp	Leu	Ser	Val	Val	Val</										

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Thr	Arg	Met	Phe	Leu	Lys	Val	Arg	Glu	Ser	Asn	Thr	Thr	Glu	Cys	Asp
945					950					955					960
Ser	Lys	Ile	Ile	Gly	Thr	Ala	Val	Lys	Asn	Asn	Leu	Ala	Ile	His	Ser
				965					970					975	
Asp	Leu	Ser	Tyr	Trp	Ile	Glu	Ser	Arg	Leu	Asn	Asp	Thr	Trp	Lys	Leu
			980					985					990		
Glu	Arg	Ala	Val	Leu	Gly	Glu	Val	Lys	Ser	Cys	Thr	Trp	Pro	Glu	Thr
		995					1000					1005			
His	Thr	Leu	Trp	Gly	Asp	Gly	Ile	Leu	Glu	Ser	Asp	Leu	Ile	Ile	
	1010					1015						1020			
Pro	Val	Thr	Leu	Ala	Gly	Pro	Arg	Ser	Asn	His	Asn	Arg	Arg	Pro	
	1025					1030						1035			
Gly	Tyr	Lys	Thr	Gln	Asn	Gln	Gly	Pro	Trp	Asp	Glu	Gly	Arg	Val	
	1040					1045					1050				
Glu	Ile	Asp	Phe	Asp	Tyr	Cys	Pro	Gly	Thr	Thr	Val	Thr	Leu	Ser	
	1055					1060					1065				
Glu	Ser	Cys	Gly	His	Arg	Gly	Pro	Ala	Thr	Arg	Thr	Thr	Thr	Glu	
	1070					1075					1080				
Ser	Gly	Lys	Leu	Ile	Thr	Asp	Trp	Cys	Cys	Arg	Ser	Cys	Thr	Leu	
	1085					1090					1095				
Pro	Pro	Leu	Arg	Tyr	Gln	Thr	Asp	Ser	Gly	Cys	Trp	Tyr	Gly	Met	
	1100					1105						1110			
Glu	Ile	Arg	Pro	Gln	Arg	His	Asp	Glu	Lys	Thr	Leu	Val	Gln	Ser	
	1115					1120					1125				
Gln	Val	Asn	Ala	Tyr	Asn	Ala	Asp	Met	Ile	Asp	Pro	Phe	Gln	Leu	
	1130					1135					1140				
Gly	Leu	Leu	Val	Val	Phe	Leu	Ala	Thr	Gln	Glu	Val	Leu	Arg	Lys	
	1145					1150					1155				
Arg	Trp	Thr	Ala	Lys	Ile	Ser	Met	Pro	Ala	Ile	Leu	Ile	Ala	Leu	
	1160					1165					1170				
Leu	Val	Leu	Val	Phe	Gly	Gly	Ile	Thr	Tyr	Thr	Asp	Val	Leu	Arg	
	1175					1180					1185				
Tyr	Val	Ile	Leu	Val	Gly	Ala	Ala	Phe	Ala	Glu	Ser	Asn	Ser	Gly	
	1190					1195					1200				
Gly	Asp	Val	Val	His	Leu	Ala	Leu	Met	Ala	Thr	Phe	Lys	Ile	Gln	
	1205					1210					1215				
Pro	Val	Phe	Met	Val	Ala	Ser	Phe	Leu	Lys	Ala	Arg	Trp	Thr	Asn	
	1220					1225					1230				
Gln	Glu	Asn	Ile	Leu	Leu	Met	Leu	Ala	Ala	Val	Phe	Phe	Gln	Met	
	1235					1240					1245				
Ala	Tyr	Tyr	Asp	Ala	Arg	Gln	Ile	Leu	Leu	Trp	Glu	Ile	Pro	Asp	
	1250					1255					1260				
Val	Leu	Asn	Ser	Leu	Ala	Val	Ala	Trp	Met	Ile	Leu	Arg	Ala	Ile	
	1265					1270					1275				
Thr	Phe	Thr	Thr	Thr	Ser	Asn	Val	Val	Val	Pro	Leu	Leu	Ala	Leu	
	1280					1285					1290				
Leu	Thr	Pro	Gly	Leu	Arg	Cys	Leu	Asn	Leu	Asp	Val	Tyr	Arg	Ile	
	1295					1300					1305				
Leu	Leu	Leu	Met	Val	Gly	Ile	Gly	Ser	Leu	Ile	Arg	Glu	Lys	Arg	
	1310					1315					1320				
Ser	Ala	Ala	Ala	Lys	Lys	Lys	Gly	Ala	Ser	Leu	Leu	Cys	Leu	Ala	
	1325					1330					1335				
Leu	Ala	Ser	Thr	Gly	Leu	Phe	Asn	Pro	Met	Ile	Leu	Ala	Ala	Gly	

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1340	1345	1350
Leu Ile Ala Cys Asp Pro	Asn Arg Lys Arg Gly Trp	Pro Ala Thr
1355	1360	1365
Glu Val Met Thr Ala Val	Gly Leu Met Phe Ala Ile	Val Gly Gly
1370	1375	1380
Leu Ala Glu Leu Asp Ile	Asp Ser Met Ala Ile Pro	Met Thr Ile
1385	1390	1395
Ala Gly Leu Met Phe Ala	Ala Phe Val Ile Ser Gly	Lys Ser Thr
1400	1405	1410
Asp Met Trp Ile Glu Arg	Thr Ala Asp Ile Ser Trp	Glu Ser Asp
1415	1420	1425
Ala Glu Ile Thr Gly Ser	Ser Glu Arg Val Asp Val	Arg Leu Asp
1430	1435	1440
Asp Asp Gly Asn Phe Gln	Leu Met Asn Asp Pro Gly	Ala Pro Trp
1445	1450	1455
Lys Ile Trp Met Leu Arg	Met Val Cys Leu Ala Ile	Ser Ala Tyr
1460	1465	1470
Thr Pro Trp Ala Ile Leu	Pro Ser Val Val Gly Phe	Trp Ile Thr
1475	1480	1485
Leu Gln Tyr Thr Lys Arg	Gly Gly Val Leu Trp Asp	Thr Pro Ser
1490	1495	1500
Pro Lys Glu Tyr Lys Lys	Gly Asp Thr Thr Thr Gly	Val Tyr Arg
1505	1510	1515
Ile Met Thr Arg Gly Leu	Leu Gly Ser Tyr Gln Ala	Gly Ala Gly
1520	1525	1530
Val Met Val Glu Gly Val	Phe His Thr Leu Trp His	Thr Thr Lys
1535	1540	1545
Gly Ala Ala Leu Met Ser	Gly Glu Gly Arg Leu Asp	Pro Tyr Trp
1550	1555	1560
Gly Ser Val Lys Glu Asp	Arg Leu Cys Tyr Gly Gly	Pro Trp Lys
1565	1570	1575
Leu Gln His Lys Trp Asn	Gly Gln Asp Glu Val Gln	Met Ile Val
1580	1585	1590
Val Glu Pro Gly Arg Asn	Val Lys Asn Val Gln Thr	Lys Pro Gly
1595	1600	1605
Val Phe Lys Thr Pro Glu	Gly Glu Ile Gly Ala Val	Thr Leu Asp
1610	1615	1620
Phe Pro Thr Gly Thr Ser	Gly Ser Pro Ile Val Asp	Lys Asn Gly
1625	1630	1635
Asp Val Ile Gly Leu Tyr	Gly Asn Gly Val Ile Met	Pro Asn Gly
1640	1645	1650
Ser Tyr Ile Ser Ala Ile	Val Gln Gly Glu Arg Met	Asp Glu Pro
1655	1660	1665
Ile Pro Ala Gly Phe Glu	Pro Glu Met Leu Arg Lys	Lys Gln Ile
1670	1675	1680
Thr Val Leu Asp Leu His	Pro Gly Ala Gly Lys Thr	Arg Arg Ile
1685	1690	1695
Leu Pro Gln Ile Ile Lys	Glu Ala Ile Asn Arg Arg	Leu Arg Thr
1700	1705	1710
Ala Val Leu Ala Pro Thr	Arg Val Val Ala Ala Glu	Met Ala Glu
1715	1720	1725
Ala Leu Arg Gly Leu Pro	Ile Arg Tyr Gln Thr Ser	Ala Val Pro
1730	1735	1740

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Arg Glu	His Asn Gly Asn Glu	Ile Val Asp Val Met	Cys His Ala
1745	1750	1755	
Thr Leu	Thr His Arg Leu Met	Ser Pro His Arg Val	Pro Asn Tyr
1760	1765	1770	
Asn Leu	Phe Val Met Asp Glu	Ala His Phe Thr Asp	Pro Ala Ser
1775	1780	1785	
Ile Ala	Ala Arg Gly Tyr Ile	Ser Thr Lys Val Glu	Leu Gly Glu
1790	1795	1800	
Ala Ala	Ala Ile Phe Met Thr	Ala Thr Pro Pro Gly	Thr Ser Asp
1805	1810	1815	
Pro Phe	Pro Glu Ser Asn Ser	Pro Ile Ser Asp Leu	Gln Thr Glu
1820	1825	1830	
Ile Pro	Asp Arg Ala Trp Asn	Ser Gly Tyr Glu Trp	Ile Thr Glu
1835	1840	1845	
Tyr Thr	Gly Lys Thr Val Trp	Phe Val Pro Ser Val	Lys Met Gly
1850	1855	1860	
Asn Glu	Ile Ala Leu Cys Leu	Gln Arg Ala Gly Lys	Lys Val Val
1865	1870	1875	
Gln Leu	Asn Arg Lys Ser Tyr	Glu Thr Glu Tyr Pro	Lys Cys Lys
1880	1885	1890	
Asn Asp	Asp Trp Asp Phe Val	Ile Thr Thr Asp Ile	Ser Glu Met
1895	1900	1905	
Gly Ala	Asn Phe Lys Ala Ser	Arg Val Ile Asp Ser	Arg Lys Ser
1910	1915	1920	
Val Lys	Pro Thr Ile Ile Thr	Glu Gly Glu Gly Arg	Val Ile Leu
1925	1930	1935	
Gly Glu	Pro Ser Ala Val Thr	Ala Ala Ser Ala Ala	Gln Arg Arg
1940	1945	1950	
Gly Arg	Ile Gly Arg Asn Pro	Ser Gln Val Gly Asp	Glu Tyr Cys
1955	1960	1965	
Tyr Gly	Gly His Thr Asn Glu	Asp Asp Ser Asn Phe	Ala His Trp
1970	1975	1980	
Thr Glu	Ala Arg Ile Met Leu	Asp Asn Ile Asn Met	Pro Asn Gly
1985	1990	1995	
Leu Ile	Ala Gln Phe Tyr Gln	Pro Glu Arg Glu Lys	Val Tyr Thr
2000	2005	2010	
Met Asp	Gly Glu Tyr Arg Leu	Arg Gly Glu Glu Arg	Lys Asn Phe
2015	2020	2025	
Leu Glu	Leu Leu Arg Thr Ala	Asp Leu Pro Val Trp	Leu Ala Tyr
2030	2035	2040	
Lys Val	Ala Ala Ala Gly Val	Ser Tyr His Asp Arg	Arg Trp Cys
2045	2050	2055	
Phe Asp	Gly Pro Arg Thr Asn	Thr Ile Leu Glu Asp	Asn Asn Glu
2060	2065	2070	
Val Glu	Val Ile Thr Lys Leu	Gly Glu Arg Lys Ile	Leu Arg Pro
2075	2080	2085	
Arg Trp	Ile Asp Ala Arg Val	Tyr Ser Asp His Gln	Ala Leu Lys
2090	2095	2100	
Ala Phe	Lys Asp Phe Ala Ser	Gly Lys Arg Ser Gln	Ile Gly Leu
2105	2110	2115	
Ile Glu	Val Leu Gly Lys Met	Pro Glu His Phe Met	Gly Lys Thr
2120	2125	2130	
Trp Glu	Ala Leu Asp Thr Met	Tyr Val Val Ala Thr	Ala Glu Lys
2135	2140	2145	

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Gly Gly 2150	Arg Ala His Arg Met 2155	Ala Leu Glu Glu Leu 2160	Pro Asp Ala
Leu Gln 2165	Thr Ile Ala Leu Ile 2170	Ala Leu Leu Ser Val 2175	Met Thr Met
Gly Val 2180	Phe Phe Leu Leu Met 2185	Gln Arg Lys Gly Ile 2190	Gly Lys Ile
Gly Leu 2195	Gly Gly Ala Val Leu 2200	Gly Val Ala Thr Phe 2205	Phe Cys Trp
Met Ala 2210	Glu Val Pro Gly Thr 2215	Lys Ile Ala Gly Met 2220	Leu Leu Leu
Ser Leu 2225	Leu Leu Met Ile Val 2230	Leu Ile Pro Glu Pro 2235	Glu Lys Gln
Arg Ser 2240	Gln Thr Asp Asn Gln 2245	Leu Ala Val Phe Leu 2250	Ile Cys Val
Met Thr 2255	Leu Val Ser Ala Val 2260	Ala Ala Asn Glu Met 2265	Gly Trp Leu
Asp Lys 2270	Thr Lys Ser Asp Ile 2275	Ser Ser Leu Phe Gly 2280	Gln Arg Ile
Glu Val 2285	Lys Glu Asn Phe Ser 2290	Met Gly Glu Phe Leu 2295	Leu Asp Leu
Arg Pro 2300	Ala Thr Ala Trp Ser 2305	Leu Tyr Ala Val Thr 2310	Thr Ala Val
Leu Thr 2315	Pro Leu Leu Lys His 2320	Leu Ile Thr Ser Asp 2325	Tyr Ile Asn
Thr Ser 2330	Leu Thr Ser Ile Asn 2335	Val Gln Ala Ser Ala 2340	Leu Phe Thr
Leu Ala 2345	Arg Gly Phe Pro Phe 2350	Val Asp Val Gly Val 2355	Ser Ala Leu
Leu Leu 2360	Ala Ala Gly Cys Trp 2365	Gly Gln Val Thr Leu 2370	Thr Val Thr
Val Thr 2375	Ala Ala Thr Leu Leu 2380	Phe Cys His Tyr Ala 2385	Tyr Met Val
Pro Gly 2390	Trp Gln Ala Glu Ala 2395	Met Arg Ser Ala Gln 2400	Arg Arg Thr
Ala Ala 2405	Gly Ile Met Lys Asn 2410	Ala Val Val Asp Gly 2415	Ile Val Ala
Thr Asp 2420	Val Pro Glu Leu Glu 2425	Arg Thr Thr Pro Ile 2430	Met Gln Lys
Lys Val 2435	Gly Gln Ile Met Leu 2440	Ile Leu Val Ser Leu 2445	Ala Ala Val
Val Val 2450	Asn Pro Ser Val Lys 2455	Thr Val Arg Glu Ala 2460	Gly Ile Leu
Ile Thr 2465	Ala Ala Ala Val Thr 2470	Leu Trp Glu Asn Gly 2475	Ala Ser Ser
Val Trp 2480	Asn Ala Thr Thr Ala 2485	Ile Gly Leu Cys His 2490	Ile Met Arg
Gly Gly 2495	Trp Leu Ser Cys Leu 2500	Ser Ile Thr Trp Thr 2505	Leu Ile Lys
Asn Met 2510	Glu Lys Pro Gly Leu 2515	Lys Arg Gly Gly Ala 2520	Lys Gly Arg
Thr Leu 2525	Gly Glu Val Trp Lys 2530	Glu Arg Leu Asn Gln 2535	Met Thr Lys
Glu Glu	Phe Thr Arg Tyr Arg	Lys Glu Ala Ile Ile	Glu Val Asp

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Arg Ser Ala Ala Lys His 2555	Ala Arg Lys Glu Gly 2560	Asn Val Thr Gly 2565
Gly His Pro Val Ser Arg 2570	Gly Thr Ala Lys Leu 2575	Arg Trp Leu Val 2580
Glu Arg Arg Phe Leu Glu 2585	Pro Val Gly Lys Val 2590	Ile Asp Leu Gly 2595
Cys Gly Arg Gly Gly Trp 2600	Cys Tyr Tyr Met Ala 2605	Thr Gln Lys Arg 2610
Val Gln Glu Val Arg Gly 2615	Tyr Thr Lys Gly Gly 2620	Pro Gly His Glu 2625
Glu Pro Gln Leu Val Gln 2630	Ser Tyr Gly Trp Asn 2635	Ile Val Thr Met 2640
Lys Ser Gly Val Asp Val 2645	Phe Tyr Arg Pro Ser 2650	Glu Cys Cys Asp 2655
Thr Leu Leu Cys Asp Ile 2660	Gly Glu Ser Ser Ser 2665	Ser Ala Glu Val 2670
Glu Glu His Arg Thr Ile 2675	Arg Val Leu Glu Met 2680	Val Glu Asp Trp 2685
Leu His Arg Gly Pro Arg 2690	Glu Phe Cys Val Lys 2695	Val Leu Cys Pro 2700
Tyr Met Pro Lys Val Ile 2705	Glu Lys Met Glu Leu 2710	Leu Gln Arg Arg 2715
Tyr Gly Gly Gly Leu Val 2720	Arg Asn Pro Leu Ser 2725	Arg Asn Ser Thr 2730
His Glu Met Tyr Trp Val 2735	Ser Arg Ala Ser Gly 2740	Asn Val Val His 2745
Ser Val Asn Met Thr Ser 2750	Gln Val Leu Leu Gly 2755	Arg Met Glu Lys 2760
Arg Thr Trp Lys Gly Pro 2765	Gln Tyr Glu Glu Asp 2770	Val Asn Leu Gly 2775
Ser Gly Thr Arg Ala Val 2780	Gly Lys Pro Leu Leu 2785	Asn Ser Asp Thr 2790
Ser Lys Ile Lys Asn Arg 2795	Ile Glu Arg Leu Arg 2800	Arg Glu Tyr Ser 2805
Ser Thr Trp His His Asp 2810	Glu Asn His Pro Tyr 2815	Arg Thr Trp Asn 2820
Tyr His Gly Ser Tyr Asp 2825	Val Lys Pro Thr Gly 2830	Ser Ala Ser Ser 2835
Leu Val Asn Gly Val Val 2840	Arg Leu Leu Ser Lys 2845	Pro Trp Asp Thr 2850
Ile Thr Asn Val Thr Thr 2855	Met Ala Met Thr Asp 2860	Thr Thr Pro Phe 2865
Gly Gln Gln Arg Val Phe 2870	Lys Glu Lys Val Asp 2875	Thr Lys Ala Pro 2880
Glu Pro Pro Glu Gly Val 2885	Lys Tyr Val Leu Asn 2890	Glu Thr Thr Asn 2895
Trp Leu Trp Ala Phe Leu 2900	Ala Arg Glu Lys Arg 2905	Pro Arg Met Cys 2910
Ser Arg Glu Glu Phe Ile 2915	Arg Lys Val Asn Ser 2920	Asn Ala Ala Leu 2925
Gly Ala Met Phe Glu Glu 2930	Gln Asn Gln Trp Arg 2935	Ser Ala Arg Glu 2940

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Ala Val 2945	Glu Asp Pro Lys Phe 2950	Trp Glu Met Val Asp 2955	Glu Glu Arg
Glu Ala 2960	His Leu Arg Gly Glu 2965	Cys His Thr Cys Ile 2970	Tyr Asn Met
Met Gly 2975	Lys Arg Glu Lys Lys 2980	Pro Gly Glu Phe Gly 2985	Lys Ala Lys
Gly Ser 2990	Arg Ala Ile Trp Phe 2995	Met Trp Leu Gly Ala 3000	Arg Phe Leu
Glu Phe 3005	Glu Ala Leu Gly Phe 3010	Leu Asn Glu Asp His 3015	Trp Leu Gly
Arg Lys 3020	Asn Ser Gly Gly Glu 3025	Val Glu Gly Leu Gly 3030	Leu Gln Lys
Leu Gly 3035	Tyr Ile Leu Arg Glu 3040	Val Gly Thr Arg Pro 3045	Gly Gly Lys
Ile Tyr 3050	Ala Asp Asp Thr Ala 3055	Gly Trp Asp Thr Arg 3060	Ile Thr Arg
Ala Asp 3065	Leu Glu Asn Glu Ala 3070	Lys Val Leu Glu Leu 3075	Leu Asp Gly
Glu His 3080	Arg Arg Leu Ala Arg 3085	Ala Ile Ile Glu Leu 3090	Thr Tyr Arg
His Lys 3095	Val Val Lys Val Met 3100	Arg Pro Ala Ala Asp 3105	Gly Arg Thr
Val Met 3110	Asp Val Ile Ser Arg 3115	Glu Asp Gln Arg Gly 3120	Ser Gly Gln
Val Val 3125	Thr Tyr Ala Leu Asn 3130	Thr Phe Thr Asn Leu 3135	Ala Val Gln
Leu Val 3140	Arg Met Met Glu Gly 3145	Glu Gly Val Ile Gly 3150	Pro Asp Asp
Val Glu 3155	Lys Leu Thr Lys Gly 3160	Lys Gly Pro Lys Val 3165	Arg Thr Trp
Leu Phe 3170	Glu Asn Gly Glu Glu 3175	Arg Leu Ser Arg Met 3180	Ala Val Ser
Gly Asp 3185	Asp Cys Val Val Lys 3190	Pro Leu Asp Asp Arg 3195	Phe Ala Thr
Ser Leu 3200	His Phe Leu Asn Ala 3205	Met Ser Lys Val Arg 3210	Lys Asp Ile
Gln Glu 3215	Trp Lys Pro Ser Thr 3220	Gly Trp Tyr Asp Trp 3225	Gln Gln Val
Pro Phe 3230	Cys Ser Asn His Phe 3235	Thr Glu Leu Ile Met 3240	Lys Asp Gly
Arg Thr 3245	Leu Val Val Pro Cys 3250	Arg Gly Gln Asp Glu 3255	Leu Val Gly
Arg Ala 3260	Arg Ile Ser Pro Gly 3265	Ala Gly Trp Asn Val 3270	Arg Asp Thr
Ala Cys 3275	Leu Ala Lys Ser Tyr 3280	Ala Gln Met Trp Leu 3285	Leu Leu Tyr
Phe His 3290	Arg Arg Asp Leu Arg 3295	Leu Met Ala Asn Ala 3300	Ile Cys Ser
Ala Val 3305	Pro Val Asn Trp Val 3310	Pro Thr Gly Arg Thr 3315	Thr Trp Ser
Ile His 3320	Ala Gly Gly Glu Trp 3325	Met Thr Thr Glu Asp 3330	Met Leu Glu
Val Trp 3335	Asn Arg Val Trp Ile 3340	Glu Glu Asn Glu Trp 3345	Met Glu Asp

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Lys Thr Pro Val Glu Lys Trp Ser Asp Val Pro Tyr Ser Gly Lys
 3350 3355 3360

Arg Glu Asp Ile Trp Cys Gly Ser Leu Ile Gly Thr Arg Ala Arg
 3365 3370 3375

Ala Thr Trp Ala Glu Asn Ile Gln Val Ala Ile Asn Gln Val Arg
 3380 3385 3390

Ala Ile Ile Gly Asp Glu Lys Tyr Val Asp Tyr Met Ser Ser Leu
 3395 3400 3405

Lys Arg Tyr Glu Asp Thr Thr Leu Val Glu Asp Thr Val Leu
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 Met Ser Lys Lys Pro Gly
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 Gly Pro Gly Lys Ser Arg Ala Val Asn Met Leu Lys Arg Gly Met Pro
 10 15 20

cgc gtg ttg tcc ttg att gga ctg aag agg gct atg ttg agc ctg atc 210
 Arg Val Leu Ser Leu Ile Gly Leu Lys Arg Ala Met Leu Ser Leu Ile
 25 30 35

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 Asp Gly Lys Gly Pro Ile Arg Phe Val Leu Ala Leu Leu Ala Phe Phe
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 Arg Phe Thr Ala Ile Ala Pro Thr Arg Ala Val Leu Asp Arg Trp Arg
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 Gly Val Asn Lys Gln Thr Ala Met Lys His Leu Leu Ser Phe Lys Lys
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 Glu Leu Gly Thr Leu Thr Ser Ala Ile Asn Arg Arg Ser Ser Lys Gln
 90 95 100

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 Lys Lys Arg Thr Ser Leu Cys Leu Met Met Met Leu Pro Ala Thr Leu
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 Ala Phe His Leu Thr Ser Arg Asp Gly Glu Pro Arg Met Ile Val Gly
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gaa gcc att tta cct gaa tat gga acc ctc ggg cta gaa tgc tca cca Glu Ala Ile Leu Pro Glu Tyr Gly Thr Leu Gly Leu Glu Cys Ser Pro 455 460 465 470	1506
cgg aca ggt ttg gat ttc aat gaa atg atc tca ttg aca atg aag aac Arg Thr Gly Leu Asp Phe Asn Glu Met Ile Ser Leu Thr Met Lys Asn 475 480 485	1554
aaa gca tgg atg gta cat aga caa tgg ttc ttt gac tta ccc cta cca Lys Ala Trp Met Val His Arg Gln Trp Phe Phe Asp Leu Pro Leu Pro 490 495 500	1602

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tgg aca tca gga gct aca gca gaa aca cca act tgg aac agg aaa gag	1650
Trp Thr Ser Gly Ala Thr Ala Glu Thr Pro Thr Trp Asn Arg Lys Glu	
505 510 515	
ctt ctt gtg aca ttt aaa aat gca cat gca aaa aag caa gaa gta gtt	1698
Leu Leu Val Thr Phe Lys Asn Ala His Ala Lys Lys Gln Glu Val Val	
520 525 530	
gtt ctt gga tca caa gag gga gca atg cat aca gca ctg aca gga gct	1746
Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu Thr Gly Ala	
535 540 545 550	
aca gag atc caa acc tca gga ggc aca agt atc ttt gcg ggg cac tta	1794
Thr Glu Ile Gln Thr Ser Gly Gly Thr Ser Ile Phe Ala Gly His Leu	
555 560 565	
aaa tgt aga ctc aag atg gac aaa ttg gaa ctc aag ggg atg agc tat	1842
Lys Cys Arg Leu Lys Met Asp Lys Leu Glu Leu Lys Gly Met Ser Tyr	
570 575 580	
gca atg tgc ttg agt agc ttt gtg ttg aag aaa gaa gtc tcc gaa acg	1890
Ala Met Cys Leu Ser Ser Phe Val Leu Lys Lys Glu Val Ser Glu Thr	
585 590 595	
cag cat ggg aca ata ctc att aag gtt gag tac aaa ggg gaa gat gca	1938
Gln His Gly Thr Ile Leu Ile Lys Val Glu Tyr Lys Gly Glu Asp Ala	
600 605 610	
ccc tgc aag att cct ttc tcc acg gag gat gga caa gga aaa gct cac	1986
Pro Cys Lys Ile Pro Phe Ser Thr Glu Asp Gly Gln Gly Lys Ala His	
615 620 625 630	
aat ggc aga ctg atc aca gcc aat cca gtg gtg acc aag aag gag gag	2034
Asn Gly Arg Leu Ile Thr Ala Asn Pro Val Val Thr Lys Lys Glu Glu	
635 640 645	
cct gtc aac att gag gct gaa cct cct ttt gga gaa agt aac ata gta	2082
Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Glu Ser Asn Ile Val	
650 655 660	
att gga att gga gac aaa gcc ctg aaa atc aac tgg tac aag aag gga	2130
Ile Gly Ile Gly Asp Lys Ala Leu Lys Ile Asn Trp Tyr Lys Lys Gly	
665 670 675	
agc tcg att ggg aag atg ttc gag gcc act gcc aga ggt gca agg cgc	2178
Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly Ala Arg Arg	
680 685 690	
atg gcc atc ttg gga gac aca gcc tgg gac ttt gga tca gtg ggt ggt	2226
Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser Val Gly Gly	
695 700 705 710	
gtt ttg aat tca tta ggg aaa atg gtc cac caa ata ttt ggg agt gct	2274
Val Leu Asn Ser Leu Gly Lys Met Val His Gln Ile Phe Gly Ser Ala	
715 720 725	
tac aca gcc cta ttt ggt gga gtc tcc tgg atg atg aaa att gga ata	2322
Tyr Thr Ala Leu Phe Gly Gly Val Ser Trp Met Met Lys Ile Gly Ile	
730 735 740	
ggg gtc ctc tta acc tgg ata ggg ttg aac tca aaa aat act tct atg	2370
Gly Val Leu Leu Thr Trp Ile Gly Leu Asn Ser Lys Asn Thr Ser Met	
745 750 755	
tca ttt tca tgc atc gcg ata gga atc att aca ctc tat ctg gga gcc	2418
Ser Phe Ser Cys Ile Ala Ile Gly Ile Ile Thr Leu Tyr Leu Gly Ala	
760 765 770	
gtg gtg caa gct gac tcc gga tgt gcc ata gac atc agc cgg caa gag	2466
Val Val Gln Ala Asp Ser Gly Cys Ala Ile Asp Ile Ser Arg Gln Glu	
775 780 785 790	
ctg aga tgt gga agt gga gtg ttc ata cac aat gat gtg gag gct tgg	2514
Leu Arg Cys Gly Ser Gly Val Phe Ile His Asn Asp Val Glu Ala Trp	
795 800 805	
atg gac cgg tac aag tat tac cct gaa acg cca caa ggc cta gcc aag	2562
Met Asp Arg Tyr Lys Tyr Tyr Pro Glu Thr Pro Gln Gly Leu Ala Lys	
810 815 820	

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atc att cag aaa gct cat aag gaa gga gtg tgc ggt cta cga tca gtt Ile Ile Gln Lys Ala His Lys Glu Gly Val Cys Gly Leu Arg Ser Val 825 830 835	2610
tcc aga ctg gag cat caa atg tgg gaa gca gtg aag gac gag ctg aac Ser Arg Leu Glu His Gln Met Trp Glu Ala Val Lys Asp Glu Leu Asn 840 845 850	2658
act ctt ttg aag gag aat ggt gtg gac ctt agt gtc gtg gtt gag aaa Thr Leu Leu Lys Glu Asn Gly Val Asp Leu Ser Val Val Val Glu Lys 855 860 865 870	2706
cag gag gga atg tac aag tca gca cct aaa cgc ctc acc gcc acc acg Gln Glu Gly Met Tyr Lys Ser Ala Pro Lys Arg Leu Thr Ala Thr Thr 875 880 885	2754
gaa aaa ttg gaa att ggc tgg aag gcc tgg gga aag agt att tta ttt Glu Lys Leu Glu Ile Gly Trp Lys Ala Trp Gly Lys Ser Ile Leu Phe 890 895 900	2802
gca cca gaa ctc gcc aac aac acc ttt gtg gtt gat ggt ccg gag acc Ala Pro Glu Leu Ala Asn Asn Thr Phe Val Val Asp Gly Pro Glu Thr 905 910 915	2850
aag gaa tgt ccg act cag aat cgc gct tgg aat agc tta gaa gtg gag Lys Glu Cys Pro Thr Gln Asn Arg Ala Trp Asn Ser Leu Glu Val Glu 920 925 930	2898
gat ttt gga ttt ggt ctc acc agc act cgg atg ttc ctg aag gtc aga Asp Phe Gly Phe Gly Leu Thr Ser Thr Arg Met Phe Leu Lys Val Arg 935 940 945 950	2946
gag agc aac aca act gaa tgt gac tcg aag atc att gga acg gct gtc Glu Ser Asn Thr Thr Glu Cys Asp Ser Lys Ile Ile Gly Thr Ala Val 955 960 965	2994
aag aac aac ttg gcg atc cac agt gac ctg tcc tat tgg att gaa agc Lys Asn Asn Leu Ala Ile His Ser Asp Leu Ser Tyr Trp Ile Glu Ser 970 975 980	3042
agg ctc aat gat acg tgg aag ctt gaa agg gca gtt ctg ggt gaa gtc Arg Leu Asn Asp Thr Trp Lys Leu Glu Arg Ala Val Leu Gly Glu Val 985 990 995	3090
aaa tca tgt acg tgg cct gag acg cat acc ttg tgg ggc gat gga Lys Ser Cys Thr Trp Pro Glu Thr His Thr Leu Trp Gly Asp Gly 1000 1005 1010	3135
atc ctt gag agt gac ttg ata ata cca gtc aca ctg gcg gga cca Ile Leu Glu Ser Asp Leu Ile Ile Pro Val Thr Leu Ala Gly Pro 1015 1020 1025	3180
cga agc aat cac aat cgg aga cct ggg tac aag aca caa aac cag Arg Ser Asn His Asn Arg Arg Pro Gly Tyr Lys Thr Gln Asn Gln 1030 1035 1040	3225
ggc cca tgg gac gaa ggc cgg gta gag att gac ttc gat tac tgc Gly Pro Trp Asp Glu Gly Arg Val Glu Ile Asp Phe Asp Tyr Cys 1045 1050 1055	3270
cca gga act acg gtc acc ctg agt gag agc tgc gga cac cgt gga Pro Gly Thr Thr Val Thr Leu Ser Glu Ser Cys Gly His Arg Gly 1060 1065 1070	3315
cct gcc act cgc acc acc aca gag agc gga aag ttg ata aca gat Pro Ala Thr Arg Thr Thr Thr Glu Ser Gly Lys Leu Ile Thr Asp 1075 1080 1085	3360
tgg tgc tgc agg agc tgc acc tta cca cca ctg cgc tac caa act Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr Gln Thr 1090 1095 1100	3405
gac agc ggc tgt tgg tat ggt atg gag atc aga cca cag aga cat Asp Ser Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Gln Arg His 1105 1110 1115	3450
gat gaa aag acc ctc gtg cag tca caa gtg aat gct tat aat gct Asp Glu Lys Thr Leu Val Gln Ser Gln Val Asn Ala Tyr Asn Ala 1120 1125 1130	3495

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gat atg	att gac cct ttt cag	ttg ggc ctt ctg gtc	gtg ttc ttg	3540
Asp Met	Ile Asp Pro Phe Gln	Leu Gly Leu Leu Val	Val Phe Leu	
1135	1140	1145		
gcc acc	cag gag gtc ctt cgc	aag agg tgg aca gcc	aag atc agc	3585
Ala Thr	Gln Glu Val Leu Arg	Lys Arg Trp Thr Ala	Lys Ile Ser	
1150	1155	1160		
atg cca	gct ata ctg att gct	ctg cta gtc ctg gtg	ttt ggg ggc	3630
Met Pro	Ala Ile Leu Ile Ala	Leu Leu Val Leu Val	Phe Gly Gly	
1165	1170	1175		
att act	tac act gat gtg tta	cgc tat gtc atc ttg	gtg ggg gca	3675
Ile Thr	Tyr Thr Asp Val Leu	Arg Tyr Val Ile Leu	Val Gly Ala	
1180	1185	1190		
gct ttc	gca gaa tct aat tcg	gga gga gac gtg gta	cac ttg gcg	3720
Ala Phe	Ala Glu Ser Asn Ser	Gly Gly Asp Val Val	His Leu Ala	
1195	1200	1205		
ctc atg	gcg acc ttc aag ata	caa cca gtg ttt atg	gtg gca tcg	3765
Leu Met	Ala Thr Phe Lys Ile	Gln Pro Val Phe Met	Val Ala Ser	
1210	1215	1220		
ttt ctc	aaa gcg aga tgg acc	aac cag gag aac att	ttg ttg atg	3810
Phe Leu	Lys Ala Arg Trp Thr	Asn Gln Glu Asn Ile	Leu Leu Met	
1225	1230	1235		
ttg gcg	gct gtt ttc ttt caa	atg gct tat tac gat	gcc cgc caa	3855
Leu Ala	Ala Val Phe Phe Gln	Met Ala Tyr Tyr Asp	Ala Arg Gln	
1240	1245	1250		
att ctg	ctc tgg gag atc cct	gat gtg ttg aat tca	ctg gcg gta	3900
Ile Leu	Leu Trp Glu Ile Pro	Asp Val Leu Asn Ser	Leu Ala Val	
1255	1260	1265		
gct tgg	atg ata ctg aga gcc	ata aca ttc aca acg	aca tca aac	3945
Ala Trp	Met Ile Leu Arg Ala	Ile Thr Phe Thr Thr	Thr Ser Asn	
1270	1275	1280		
gtg gtt	gtt ccg ctg cta gcc	ctg cta aca ccc ggg	ctg aga tgc	3990
Val Val	Val Pro Leu Leu Ala	Leu Leu Thr Pro Gly	Leu Arg Cys	
1285	1290	1295		
ttg aat	ctg gat gtg tac agg	ata ctg ctg ttg atg	gtc gga ata	4035
Leu Asn	Leu Asp Val Tyr Arg	Ile Leu Leu Leu Met	Val Gly Ile	
1300	1305	1310		
ggc agc	ttg atc agg gag aag	agg agt gca gct gca	aaa aag aaa	4080
Gly Ser	Leu Ile Arg Glu Lys	Arg Ser Ala Ala Ala	Lys Lys Lys	
1315	1320	1325		
gga gca	agt ctg cta tgc ttg	gct cta gcc tca aca	gga ctt ttc	4125
Gly Ala	Ser Leu Leu Cys Leu	Ala Leu Ala Ser Thr	Gly Leu Phe	
1330	1335	1340		
aac ccc	atg atc ctt gct gct	gga ctg att gca tgt	gat ccc aac	4170
Asn Pro	Met Ile Leu Ala Ala	Gly Leu Ile Ala Cys	Asp Pro Asn	
1345	1350	1355		
cgt aaa	cgc gga tgg ccc gca	act gaa gtg atg aca	gct gtc ggc	4215
Arg Lys	Arg Gly Trp Pro Ala	Thr Glu Val Met Thr	Ala Val Gly	
1360	1365	1370		
cta atg	ttt gcc atc gtc gga	ggg ctg gca gag ctt	gac att gac	4260
Leu Met	Phe Ala Ile Val Gly	Gly Leu Ala Glu Leu	Asp Ile Asp	
1375	1380	1385		
tcc atg	gcc att cca atg act	atc gcg ggg ctc atg	ttt gct gct	4305
Ser Met	Ala Ile Pro Met Thr	Ile Ala Gly Leu Met	Phe Ala Ala	
1390	1395	1400		
ttc gtg	att tct ggg aaa tca	aca gat atg tgg att	gag aga acg	4350
Phe Val	Ile Ser Gly Lys Ser	Thr Asp Met Trp Ile	Glu Arg Thr	
1405	1410	1415		
gcg gac	att tcc tgg gaa agt	gat gca gaa att aca	ggc tcg agc	4395
Ala Asp	Ile Ser Trp Glu Ser	Asp Ala Glu Ile Thr	Gly Ser Ser	
1420	1425	1430		

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gaa aga Glu Arg 1435	ggt gat gtg cgg ctt Val Asp Val Arg Leu 1440	gat gat gat gga aac Asp Asp Asp Gly Asn 1445	ttc cag ctc Phe Gln Leu 1450	4440
atg aat Met Asn 1450	gat cca gga gca cct Asp Pro Gly Ala Pro 1455	tgg aag ata tgg atg Trp Lys Ile Trp Met 1460	ctc aga atg Leu Arg Met 1465	4485
gtc tgt Val Cys 1465	ctc gcg att agt gcg Leu Ala Ile Ser Ala 1470	tac acc ccc tgg gca Tyr Thr Pro Trp Ala 1475	atc ttg ccc Ile Leu Pro 1480	4530
tca gta Ser Val 1480	ggt gga ttt tgg ata Val Gly Phe Trp Ile 1485	act ctc caa tac aca Thr Leu Gln Tyr Thr 1490	aag aga gga Lys Arg Gly 1495	4575
ggc gtg Gly Val 1495	ttg tgg gac act ccc Leu Trp Asp Thr Pro 1500	tca cca aag gag tac Ser Pro Lys Glu Tyr 1505	aaa aag ggg Lys Lys Gly 1510	4620
gac acg Asp Thr 1510	acc acc ggc gtc tac Thr Thr Gly Val Tyr 1515	agg atc atg act cgt Arg Ile Met Thr Arg 1520	ggg ctg ctc Gly Leu Leu 1525	4665
ggc agt Gly Ser 1525	tat caa gca gga gcg Tyr Gln Ala Gly Ala 1530	ggc gtg atg gtt gaa Gly Val Met Val Glu 1535	ggt gtt ttc Gly Val Phe 1540	4710
cac acc His Thr 1540	ctt tgg cat aca aca Leu Trp His Thr Thr 1545	aaa gga gcc gct ttg Lys Gly Ala Ala Leu 1550	atg agc gga Met Ser Gly 1555	4755
gag ggc Glu Gly 1555	cgc ctg gac cca tac Arg Leu Asp Pro Tyr 1560	tgg ggc agt gtc aag Trp Gly Ser Val Lys 1565	gag gat cga Glu Asp Arg 1570	4800
ctt tgt Leu Cys 1570	tac gga gga ccc tgg Tyr Gly Gly Pro Trp 1575	aaa ttg cag cac aag Lys Leu Gln His Lys 1580	tgg aac ggg Trp Asn Gly 1585	4845
cag gat Gln Asp 1585	gag gtg cag atg att Glu Val Gln Met Ile 1590	gtg gtg gaa cct ggc Val Val Glu Pro Gly 1595	agg aac gtt Arg Asn Val 1600	4890
aag aac Lys Asn 1600	gtc cag acg aaa cca Val Gln Thr Lys Pro 1605	ggg gtg ttc aaa aca Gly Val Phe Lys Thr 1610	cct gaa gga Pro Glu Gly 1615	4935
gaa atc Glu Ile 1615	ggg gcc gtg act ttg Gly Ala Val Thr Leu 1620	gac ttc ccc act gga Asp Phe Pro Thr Gly 1625	aca tca ggc Thr Ser Gly 1630	4980
tca cca Ser Pro 1630	ata gtg gac aaa aac Ile Val Asp Lys Asn 1635	ggt gat gtg att ggg Gly Asp Val Ile Gly 1640	ctt tat ggc Leu Tyr Gly 1645	5025
aat gga Asn Gly 1645	gtc ata atg ccc aac Val Ile Met Pro Asn 1650	ggc tca tac ata agc Gly Ser Tyr Ile Ser 1655	gcg ata gtg Ala Ile Val 1660	5070
cag ggt Gln Gly 1660	gaa agg atg gat gag Glu Arg Met Asp Glu 1665	cca atc cca gcc gga Pro Ile Pro Ala Gly 1670	ttc gaa cct Phe Glu Pro 1675	5115
gag atg Glu Met 1675	ctg agg aaa aaa cag Leu Arg Lys Lys Gln 1680	atc act gta ctg gat Ile Thr Val Leu Asp 1685	ctc cat ccc Leu His Pro 1690	5160
ggc gcc Gly Ala 1690	ggt aaa aca agg agg Gly Lys Thr Arg Arg 1695	att ctg cca cag atc Ile Leu Pro Gln Ile 1700	atc aaa gag Ile Lys Glu 1705	5205
gcc ata Ala Ile 1705	aac aga aga ctg aga Asn Arg Arg Leu Arg 1710	aca gcc gtg cta gca Thr Ala Val Leu Ala 1715	cca acc agg Pro Thr Arg 1720	5250
gtt gtg Val Val 1720	gct gct gag atg gct Ala Ala Glu Met Ala 1725	gaa gca ctg aga gga Glu Ala Leu Arg Gly 1730	ctg ccc atc Leu Pro Ile 1735	5295

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cgg tac Arg Tyr 1735	cag aca tcc gca gtg Gln Thr Ser Ala Val 1740	ccc aga gaa cat aat Pro Arg Glu His Asn 1745	gga aat gag Gly Asn Glu	5340
att gtt Ile Val 1750	gat gtc atg tgt cat Asp Val Met Cys His 1755	gct acc ctc acc cac Ala Thr Leu Thr His 1760	agg ctg atg Arg Leu Met	5385
tct cct Ser Pro 1765	cac agg gtg ccg aac His Arg Val Pro Asn 1770	tac aac ctg ttc gtg Tyr Asn Leu Phe Val 1775	atg gat gag Met Asp Glu	5430
gct cat Ala His 1780	ttc acc gac cca gct Phe Thr Asp Pro Ala 1785	agc att gca gca aga Ser Ile Ala Ala Arg 1790	ggt tac att Gly Tyr Ile	5475
tcc aca Ser Thr 1795	aag gtc gag cta ggg Lys Val Glu Leu Gly 1800	gag gcg gcg gca ata Glu Ala Ala Ala Ile 1805	ttc atg aca Phe Met Thr	5520
gcc acc Ala Thr 1810	cca cca ggc act tca Pro Pro Gly Thr Ser 1815	gat cca ttc cca gag Asp Pro Phe Pro Glu 1820	tcc aat tca Ser Asn Ser	5565
cca att Pro Ile 1825	tcc gac tta cag act Ser Asp Leu Gln Thr 1830	gag atc ccg gat cga Glu Ile Pro Asp Arg 1835	gct tgg aac Ala Trp Asn	5610
tct gga Ser Gly 1840	tac gaa tgg atc aca Tyr Glu Trp Ile Thr 1845	gaa tac acc ggg aag Glu Tyr Thr Gly Lys 1850	acg gtt tgg Thr Val Trp	5655
ttt gtg Phe Val 1855	cct agt gtc aag atg Pro Ser Val Lys Met 1860	ggg aat gag att gcc Gly Asn Glu Ile Ala 1865	ctt tgc cta Leu Cys Leu	5700
caa cgt Gln Arg 1870	gct gga aag aaa gta Ala Gly Lys Lys Val 1875	gtc caa ttg aac aga Val Gln Leu Asn Arg 1880	aag tcg tac Lys Ser Tyr	5745
gag acg Glu Thr 1885	gag tac cca aaa tgt Glu Tyr Pro Lys Cys 1890	aag aac gat gat tgg Lys Asn Asp Asp Trp 1895	gac ttt gtt Asp Phe Val	5790
atc aca Ile Thr 1900	aca gac ata tct gaa Thr Asp Ile Ser Glu 1905	atg ggg gct aac ttc Met Gly Ala Asn Phe 1910	aag gcg agc Lys Ala Ser	5835
agg gtg Arg Val 1915	att gac agc ccg aag Ile Asp Ser Arg Lys 1920	agt gtg aaa cca acc Ser Val Lys Pro Thr 1925	atc ata aca Ile Ile Thr	5880
gaa gga Glu Gly 1930	gaa ggg aga gtg atc Glu Gly Arg Val Ile 1935	ctg gga gaa cca tct Leu Gly Glu Pro Ser 1940	gca gtg aca Ala Val Thr	5925
gca gct Ala Ala 1945	agt gcc gcc cag aga Ser Ala Ala Gln Arg 1950	cggt gga cgt atc ggt Arg Gly Arg Ile Gly 1955	aga aat ccg Arg Asn Pro	5970
tcg caa Ser Gln 1960	gtt ggt gat gag tac Val Gly Asp Glu Tyr 1965	tgt tat ggg ggg cac Cys Tyr Gly Gly His 1970	acg aat gaa Thr Asn Glu	6015
gac gac Asp Asp 1975	tcg aac ttc gcc cat Ser Asn Phe Ala His 1980	tgg act gag gca cga Trp Thr Glu Ala Arg 1985	atc atg ctg Ile Met Leu	6060
gac aac Asp Asn 1990	atc aac atg cca aac Ile Asn Met Pro Asn 1995	gga ctg atc gct caa Gly Leu Ile Ala Gln 2000	ttc tac caa Phe Tyr Gln	6105
cca gag Pro Glu 2005	cggt gag aag gta tat Arg Glu Lys Val Tyr 2010	acc atg gat ggg gaa Thr Met Asp Gly Glu 2015	tac ccg ctc Tyr Arg Leu	6150
aga gga Arg Gly 2020	gaa gag aga aaa aac Glu Glu Arg Lys Asn 2025	ttt ctg gaa ctg ttg Phe Leu Glu Leu Leu 2030	agg act gca Arg Thr Ala	6195

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gat ctg cca gtt tgg ctg gct Asp Leu Pro Val Trp Leu Ala 2035 2040	tac aag gtt gca gcg gct gga gtg Tyr Lys Val Ala Ala Ala Gly Val 2045	6240
tca tac cac gac cgg agg tgg Ser Tyr His Asp Arg Arg Trp 2050 2055	tgc ttt gat ggt cct agg aca aac Cys Phe Asp Gly Pro Arg Thr Asn 2060	6285
aca att tta gaa gac aac aac Thr Ile Leu Glu Asp Asn Asn 2065 2070	gaa gtg gaa gtc atc acg aag ctt Glu Val Glu Val Ile Thr Lys Leu 2075	6330
ggg gaa agg aag att ctg agg Gly Glu Arg Lys Ile Leu Arg 2080 2085	cgc cgc tgg att gac gcc agg gtg Pro Arg Trp Ile Asp Ala Arg Val 2090	6375
tac tcg gat cac cag gca cta Tyr Ser Asp His Gln Ala Leu 2095 2100	aag gcg ttc aag gac ttc gcc tcg Lys Ala Phe Lys Asp Phe Ala Ser 2105	6420
gga aaa cgt tct cag ata ggg Gly Lys Arg Ser Gln Ile Gly 2110 2115	ctc att gag gtt ctg gga aag atg Leu Ile Glu Val Leu Gly Lys Met 2120	6465
cct gag cac ttc atg ggg aag Pro Glu His Phe Met Gly Lys 2125 2130	aca tgg gaa gca ctt gac acc atg Thr Trp Glu Ala Leu Asp Thr Met 2135	6510
tac gtt gtg gcc act gca gag Tyr Val Val Ala Thr Ala Glu 2140 2145	aaa gga gga aga gct cac aga atg Lys Gly Gly Arg Ala His Arg Met 2150	6555
gcc ctg gag gaa ctg cca gat Ala Leu Glu Glu Leu Pro Asp 2155 2160	gct ctt cag aca att gcc ttg att Ala Leu Gln Thr Ile Ala Leu Ile 2165	6600
gcc tta ttg agt gtg atg acc Ala Leu Leu Ser Val Met Thr 2170 2175	atg gga gta ttc ttc ctc ctc atg Met Gly Val Phe Phe Leu Leu Met 2180	6645
cag cgg aag ggc att gga aag Gln Arg Lys Gly Ile Gly Lys 2185 2190	ata ggt ttg gga ggc gct gtc ttg Ile Gly Leu Gly Gly Ala Val Leu 2195	6690
gga gtc gcg acc ttt ttc tgt Gly Val Ala Thr Phe Phe Cys 2200 2205	tgg atg gct gaa gtt cca gga acg Trp Met Ala Glu Val Pro Gly Thr 2210	6735
aag atc gcc gga atg ttg ctg Lys Ile Ala Gly Met Leu Leu 2215 2220	ctc tcc ctt ctc ttg atg att gtg Leu Ser Leu Leu Leu Met Ile Val 2225	6780
cta att cct gag cca gag aag Leu Ile Pro Glu Pro Glu Lys 2230 2235	caa cgt tcg cag aca gac aac cag Gln Arg Ser Gln Thr Asp Asn Gln 2240	6825
cta gcc gtg ttc ctg att tgt Leu Ala Val Phe Leu Ile Cys 2245 2250	gtc atg acc ctt gtg agc gca gtg Val Met Thr Leu Val Ser Ala Val 2255	6870
gca gcc aac gag atg ggt tgg Ala Ala Asn Glu Met Gly Trp 2260 2265	cta gat aag acc aag agt gac ata Leu Asp Lys Thr Lys Ser Asp Ile 2270	6915
agc agt ttg ttt ggg caa aga Ser Ser Leu Phe Gly Gln Arg 2275 2280	att gag gtc aag gag aat ttc agc Ile Glu Val Lys Glu Asn Phe Ser 2285	6960
atg gga gag ttt ctt ttg gac Met Gly Glu Phe Leu Leu Asp 2290 2295	ttg agg cct gca aca gcc tgg tca Leu Arg Pro Ala Thr Ala Trp Ser 2300	7005
ctg tac gct gtg aca aca gcg Leu Tyr Ala Val Thr Thr Ala 2305 2310	gtc ctc act cca ctg cta aag cat Val Leu Thr Pro Leu Leu Lys His 2315	7050
ttg atc acg tca gat tac atc Leu Ile Thr Ser Asp Tyr Ile 2320 2325	aac acc tca ttg acc tca ata aac Asn Thr Ser Leu Thr Ser Ile Asn 2330	7095

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ggt cag	gca agt gca cta ttc	aca ctc gcg cga ggc	ttc ccc ttc	7140
Val Gln	Ala Ser Ala Leu Phe	Thr Leu Ala Arg Gly	Phe Pro Phe	
2335	2340	2345		
gtc gat	gtt gga gtg tgg gct	ctc ctg cta gca gcc	gga tgc tgg	7185
Val Asp	Val Gly Val Ser Ala	Leu Leu Leu Ala Ala	Gly Cys Trp	
2350	2355	2360		
gga caa	gtc acc ctc acc gtt	acg gta aca gcg gca	aca ctc ctt	7230
Gly Gln	Val Thr Leu Thr Val	Thr Val Thr Ala Ala	Thr Leu Leu	
2365	2370	2375		
ttt tgc	cac tat gcc tac atg	gtt ccc ggt tgg caa	gct gag gca	7275
Phe Cys	His Tyr Ala Tyr Met	Val Pro Gly Trp Gln	Ala Glu Ala	
2380	2385	2390		
atg cgc	tca gcc cag cgg cgg	aca gcg gcc gga atc	atg aag aac	7320
Met Arg	Ser Ala Gln Arg Arg	Thr Ala Ala Gly Ile	Met Lys Asn	
2395	2400	2405		
gct gta	gtg gat gcc atc gtg	gcc acg gac gtc cca	gaa tta gag	7365
Ala Val	Val Asp Gly Ile Val	Ala Thr Asp Val Pro	Glu Leu Glu	
2410	2415	2420		
cgc acc	aca ccc atc atg cag	aag aaa gtt gga cag	atc atg ctg	7410
Arg Thr	Thr Pro Ile Met Gln	Lys Lys Val Gly Gln	Ile Met Leu	
2425	2430	2435		
atc ttg	gtg tct cta gct gca	gta gta gtg aac ccg	tct gtg aag	7455
Ile Leu	Val Ser Leu Ala Ala	Val Val Val Asn Pro	Ser Val Lys	
2440	2445	2450		
aca gta	cga gaa gcc gga att	ttg atc acg gcc gca	gcg gtg acg	7500
Thr Val	Arg Glu Ala Gly Ile	Leu Ile Thr Ala Ala	Ala Val Thr	
2455	2460	2465		
ctt tgg	gag aat gga gca agc	tct gtt tgg aac gca	aca act gcc	7545
Leu Trp	Glu Asn Gly Ala Ser	Ser Val Trp Asn Ala	Thr Thr Ala	
2470	2475	2480		
atc gga	ctc tgc cac atc atg	cgt ggg ggt tgg ttg	tca tgt cta	7590
Ile Gly	Leu Cys His Ile Met	Arg Gly Gly Trp Leu	Ser Cys Leu	
2485	2490	2495		
tcc ata	aca tgg aca ctc ata	aag aac atg gaa aaa	cca gga cta	7635
Ser Ile	Thr Trp Thr Leu Ile	Lys Asn Met Glu Lys	Pro Gly Leu	
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aaa aga	ggg gga gca aaa gga	cgc acc ttg gga gag	gtt tgg aaa	7680
Lys Arg	Gly Gly Ala Lys Gly	Arg Thr Leu Gly Glu	Val Trp Lys	
2515	2520	2525		
gaa aga	ctc aac cag atg aca	aaa gaa gag ttc act	agg tac cgc	7725
Glu Arg	Leu Asn Gln Met Thr	Lys Glu Glu Phe Thr	Arg Tyr Arg	
2530	2535	2540		
aaa gag	gcc atc atc gaa gtc	gat cgc tca gcg gca	aaa cac gcc	7770
Lys Glu	Ala Ile Ile Glu Val	Asp Arg Ser Ala Ala	Lys His Ala	
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agg aaa	gaa ggc aat gtc act	gga ggg cat cca gtc	tct agg ggc	7815
Arg Lys	Glu Gly Asn Val Thr	Gly Gly His Pro Val	Ser Arg Gly	
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aca gca	aaa ctg aga tgg ctg	gtc gaa cgg agg ttt	ctc gaa ccg	7860
Thr Ala	Lys Leu Arg Trp Leu	Val Glu Arg Arg Phe	Leu Glu Pro	
2575	2580	2585		
gtc gga	aaa gtg att gac ctt	gga tgt gga aga ggc	ggg tgg tgt	7905
Val Gly	Lys Val Ile Asp Leu	Gly Cys Gly Arg Gly	Gly Trp Cys	
2590	2595	2600		
tac tat	atg gca acc caa aaa	aga gtc caa gaa gtc	aga ggg tac	7950
Tyr Tyr	Met Ala Thr Gln Lys	Arg Val Gln Glu Val	Arg Gly Tyr	
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aca aag	ggc ggt ccc gga cat	gaa gag ccc caa cta	gtg caa agt	7995
Thr Lys	Gly Gly Pro Gly His	Glu Glu Pro Gln Leu	Val Gln Ser	
2620	2625	2630		

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tat gga	tgg aac att gtc acc	atg aag agt gga gtg	gat gtg ttc	8040
Tyr Gly	Trp Asn Ile Val Thr	Met Lys Ser Gly Val	Asp Val Phe	
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tac aga	cct tct gag tgt tgt	gac acc ctc ctt tgt	gac atc gga	8085
Tyr Arg	Pro Ser Glu Cys Cys	Asp Thr Leu Leu Cys	Asp Ile Gly	
2650	2655	2660		
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Glu Ser	Ser Ser Ser Ala Glu	Val Glu Glu His Arg	Thr Ile Arg	
2665	2670	2675		
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Val Leu	Glu Met Val Glu Asp	Trp Leu His Arg Gly	Pro Arg Glu	
2680	2685	2690		
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Phe Cys	Val Lys Val Leu Cys	Pro Tyr Met Pro Lys	Val Ile Glu	
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aag atg	gag ctg ctc caa cgc	cgg tat ggg ggg gga	ctg gtc aga	8265
Lys Met	Glu Leu Leu Gln Arg	Arg Tyr Gly Gly Gly	Leu Val Arg	
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aac cca	ctc tca cgg aat tcc	acg cac gag atg tat	tgg gtg agt	8310
Asn Pro	Leu Ser Arg Asn Ser	Thr His Glu Met Tyr	Trp Val Ser	
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Arg Ala	Ser Gly Asn Val Val	His Ser Val Asn Met	Thr Ser Gln	
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Val Leu	Leu Gly Arg Met Glu	Lys Arg Thr Trp Lys	Gly Pro Gln	
2755	2760	2765		
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Tyr Glu	Glu Asp Val Asn Leu	Gly Ser Gly Thr Arg	Ala Val Gly	
2770	2775	2780		
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Lys Pro	Leu Leu Asn Ser Asp	Thr Ser Lys Ile Lys	Asn Arg Ile	
2785	2790	2795		
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Glu Arg	Leu Arg Arg Glu Tyr	Ser Ser Thr Trp His	His Asp Glu	
2800	2805	2810		
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Asn His	Pro Tyr Arg Thr Trp	Asn Tyr His Gly Ser	Tyr Asp Val	
2815	2820	2825		
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Lys Pro	Thr Gly Ser Ala Ser	Ser Leu Val Asn Gly	Val Val Arg	
2830	2835	2840		
ctc ctc	tca aaa cca tgg gac	acc atc acg aat gtt	acc acc atg	8670
Leu Leu	Ser Lys Pro Trp Asp	Thr Ile Thr Asn Val	Thr Thr Met	
2845	2850	2855		
gcc atg	act gac act act ccc	ttc ggg cag cag cga	gtg ttc aaa	8715
Ala Met	Thr Asp Thr Thr Pro	Phe Gly Gln Gln Arg	Val Phe Lys	
2860	2865	2870		
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Glu Lys	Val Asp Thr Lys Ala	Pro Glu Pro Pro Glu	Gly Val Lys	
2875	2880	2885		
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Tyr Val	Leu Asn Glu Thr Thr	Asn Trp Leu Trp Ala	Phe Leu Ala	
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aga gaa	aaa cgt ccc aga atg	tgc tct cga gag gaa	ttc ata aga	8850
Arg Glu	Lys Arg Pro Arg Met	Cys Ser Arg Glu Glu	Phe Ile Arg	
2905	2910	2915		
aag gtc	aac agc aat gca gct	ttg ggt gcc atg ttt	gaa gag cag	8895
Lys Val	Asn Ser Asn Ala Ala	Leu Gly Ala Met Phe	Glu Glu Gln	
2920	2925	2930		

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tgg gag atg gtg gat gag gag cgc gag gca cat ctg cgg ggg gaa 8985 Trp Glu Met Val Asp Glu Glu Arg Glu Ala His Leu Arg Gly Glu 2950 2955 2960	
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ccc gga gag ttc gga aag gcc aag gga agc aga gcc att tgg ttc 9075 Pro Gly Glu Phe Gly Lys Ala Lys Gly Ser Arg Ala Ile Trp Phe 2980 2985 2990	
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ggc tgg gac acc cgc atc acg aga gct gac ttg gaa aat gaa gct 9300 Gly Trp Asp Thr Arg Ile Thr Arg Ala Asp Leu Glu Asn Glu Ala 3055 3060 3065	
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ccc ctg gac gat cgc ttt gcc acc tcg ctc cac ttc ctc aat gct 9705 Pro Leu Asp Asp Arg Phe Ala Thr Ser Leu His Phe Leu Asn Ala 3190 3195 3200	
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Arg Gly	Gln Asp	Glu Leu	Val	Gly Arg	Ala Arg	Ile	Ser Pro	Gly	
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Ala Gly	Trp Asn	Val Arg	Asp	Thr Ala	Cys Leu	Ala	Lys Ser	Tyr	
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Ala Gln	Met Trp	Leu Leu	Leu	Tyr Phe	His Arg	Arg	Asp Leu	Arg	
3280			3285			3290			
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Leu Met	Ala Asn	Ala Ile	Cys	Ser Ala	Val Pro	Val	Asn Trp	Val	
3295			3300			3305			
cct acc	gga aga	acc acg	tgg	tcc atc	cat gca	gga	gga gag	tgg	10065
Pro Thr	Gly Arg	Thr Thr	Trp	Ser Ile	His Ala	Gly	Gly Glu	Trp	
3310			3315			3320			
atg aca	aca gag	gac atg	ttg	gag gtc	tgg aac	cgt	ggt tgg	ata	10110
Met Thr	Thr Glu	Asp Met	Leu	Glu Val	Trp Asn	Arg	Val Trp	Ile	
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Glu Glu	Asn Glu	Trp Met	Glu	Asp Lys	Thr Pro	Val	Glu Lys	Trp	
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Ser Asp	Val Pro	Tyr Ser	Gly	Lys Arg	Glu Asp	Ile	Trp Cys	Gly	
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agc ctg	att ggc	aca aga	gcc	cga gcc	acg tgg	gca	gaa aac	atc	10245
Ser Leu	Ile Gly	Thr Arg	Ala	Arg Ala	Thr Trp	Ala	Glu Asn	Ile	
3370			3375			3380			
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Gln Val	Ala Ile	Asn Gln	Val	Arg Ala	Ile Ile	Gly	Asp Glu	Lys	
3385			3390			3395			
tat gtg	gat tac	atg agt	tca	cta aag	aga tat	gaa	gac aca	act	10335
Tyr Val	Asp Tyr	Met Ser	Ser	Leu Lys	Arg Tyr	Glu	Asp Thr	Thr	
3400			3405			3410			
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Leu Val	Glu Asp	Thr Val	Leu						
3415			3420						
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atct									10990

<210> SEQ ID NO 6

<211> LENGTH: 3420

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 6

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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 Thr Ser Leu Cys Leu Met Met
100         105         110

Met Leu Pro Ala Thr Leu Ala Phe His Leu Thr Ser Arg Asp Gly Glu
115         120         125

Pro Arg Met Ile Val Gly Lys Asn Glu Arg Gly Lys Ser Leu Leu Phe
130         135         140

Lys Thr Ala Ser Gly Ile Asn Met Cys Thr Leu Ile Ala Met Asp Leu
145         150         155         160

Gly Glu Met Cys Asp Asp Thr Val Thr Tyr Lys Cys Pro His Ile Thr
165         170         175

Glu Val Glu Pro Glu Asp Ile Asp Cys Trp Cys Asn Leu Thr Ser Thr
180         185         190

Trp Val Thr Tyr Gly Thr Cys Asn Gln Ala Gly Glu His Arg Arg Asp
195         200         205

Lys Arg Ser Val Ala Leu Ala Pro His Val Gly Met Gly Leu Asp Thr
210         215         220

Arg Thr Gln Thr Trp Met Ser Ala Glu Gly Ala Trp Arg Gln Val Glu
225         230         235         240

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

Leu Phe Leu Ala His Tyr Ile Gly Thr Ser Leu Thr Gln Lys Val Val
260         265         270

Ile Phe Ile Leu Leu Met Leu Val Thr Pro Ser Met Thr Met Arg Cys
275         280         285

Val Gly Val Gly Asn Arg Asp Phe Val Glu Gly Leu Ser Gly Ala Thr
290         295         300

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

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

Gln Leu Ala Thr Leu Arg Lys Leu Cys Ile Glu Gly Lys Ile Thr Asn
340         345         350

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

Glu Glu Gln Asp Gln Asn Tyr Val Cys Lys His Thr Tyr Val Asp Arg
370         375         380

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

Cys Ala Lys Phe Gln Cys Leu Glu Ser Ile Glu Gly Lys Val Val Gln

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Pro	Gln	Ala	Ser	Thr	Ala	Glu	Ala	Ile	Leu	Pro	Glu	Tyr	Gly	Thr	Leu
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Gly	Leu	Glu	Cys	Ser	Pro	Arg	Thr	Gly	Leu	Asp	Phe	Asn	Glu	Met	Ile
465								475				480			
Ser	Leu	Thr	Met	Lys	Asn	Lys	Ala	Trp	Met	Val	His	Arg	Gln	Trp	Phe
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Phe	Asp	Leu	Pro	Leu	Pro	Trp	Thr	Ser	Gly	Ala	Thr	Ala	Glu	Thr	Pro
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Thr	Trp	Asn	Arg	Lys	Glu	Leu	Leu	Val	Thr	Phe	Lys	Asn	Ala	His	Ala
515								520				525			
Lys	Lys	Gln	Glu	Val	Val	Val	Leu	Gly	Ser	Gln	Glu	Gly	Ala	Met	His
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Thr	Ala	Leu	Thr	Gly	Ala	Thr	Glu	Ile	Gln	Thr	Ser	Gly	Gly	Thr	Ser
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Ile	Phe	Ala	Gly	His	Leu	Lys	Cys	Arg	Leu	Lys	Met	Asp	Lys	Leu	Glu
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Leu	Lys	Gly	Met	Ser	Tyr	Ala	Met	Cys	Leu	Ser	Ser	Phe	Val	Leu	Lys
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Lys	Glu	Val	Ser	Glu	Thr	Gln	His	Gly	Thr	Ile	Leu	Ile	Lys	Val	Glu
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Tyr	Lys	Gly	Glu	Asp	Ala	Pro	Cys	Lys	Ile	Pro	Phe	Ser	Thr	Glu	Asp
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Gly	Gln	Gly	Lys	Ala	His	Asn	Gly	Arg	Leu	Ile	Thr	Ala	Asn	Pro	Val
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Val	Thr	Lys	Lys	Glu	Glu	Pro	Val	Asn	Ile	Glu	Ala	Glu	Pro	Pro	Phe
645								650				655			
Gly	Glu	Ser	Asn	Ile	Val	Ile	Gly	Ile	Gly	Asp	Lys	Ala	Leu	Lys	Ile
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Asn	Trp	Tyr	Lys	Lys	Gly	Ser	Ser	Ile	Gly	Lys	Met	Phe	Glu	Ala	Thr
675								680				685			
Ala	Arg	Gly	Ala	Arg	Arg	Met	Ala	Ile	Leu	Gly	Asp	Thr	Ala	Trp	Asp
690								695				700			
Phe	Gly	Ser	Val	Gly	Gly	Val	Leu	Asn	Ser	Leu	Gly	Lys	Met	Val	His
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Gln	Ile	Phe	Gly	Ser	Ala	Tyr	Thr	Ala	Leu	Phe	Gly	Gly	Val	Ser	Trp
725								730				735			
Met	Met	Lys	Ile	Gly	Ile	Gly	Val	Leu	Leu	Thr	Trp	Ile	Gly	Leu	Asn
740								745				750			
Ser	Lys	Asn	Thr	Ser	Met	Ser	Phe	Ser	Cys	Ile	Ala	Ile	Gly	Ile	Ile
755								760				765			
Thr	Leu	Tyr	Leu	Gly	Ala	Val	Val	Gln	Ala	Asp	Ser	Gly	Cys	Ala	Ile
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Asp	Ile	Ser	Arg	Gln	Glu	Leu	Arg	Cys	Gly	Ser	Gly	Val	Phe	Ile	His
785								795				800			
Asn	Asp	Val	Glu	Ala	Trp	Met	Asp	Arg	Tyr	Lys	Tyr	Tyr	Pro	Glu	Thr
805								810				815			
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Cys	Gly	Leu	Arg	Ser	Val	Ser	Arg	Leu	Glu	His	Gln	Met	Trp	Glu	Ala
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Ser	Val	Val	Val	Glu	Lys	Gln	Glu	Gly	Met	Tyr	Lys	Ser	Ala	Pro	Lys
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Arg	Leu	Thr	Ala	Thr	Thr	Glu	Lys	Leu	Glu	Ile	Gly	Trp	Lys	Ala	Trp
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Gly	Lys	Ser	Ile	Leu	Phe	Ala	Pro	Glu	Leu	Ala	Asn	Asn	Thr	Phe	Val
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Val	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	Arg
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Met	Phe	Leu	Lys	Val	Arg	Glu	Ser	Asn	Thr	Thr	Glu	Cys	Asp	Ser	Lys
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Ser	Tyr	Trp	Ile	Glu	Ser	Arg	Leu	Asn	Asp	Thr	Trp	Lys	Leu	Glu	Arg
			980					985					990		
Ala	Val	Leu	Gly	Glu	Val	Lys	Ser	Cys	Thr	Trp	Pro	Glu	Thr	His	Thr
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Leu	Trp	Gly	Asp	Gly	Ile	Leu	Glu	Ser	Asp	Leu	Ile	Ile	Pro	Val	
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Thr	Leu	Ala	Gly	Pro	Arg	Ser	Asn	His	Asn	Arg	Arg	Pro	Gly	Tyr	
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Lys	Thr	Gln	Asn	Gln	Gly	Pro	Trp	Asp	Glu	Gly	Arg	Val	Glu	Ile	
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Cys	Gly	His	Arg	Gly	Pro	Ala	Thr	Arg	Thr	Thr	Thr	Glu	Ser	Gly	
	1070					1075						1080			
Lys	Leu	Ile	Thr	Asp	Trp	Cys	Cys	Arg	Ser	Cys	Thr	Leu	Pro	Pro	
	1085					1090						1095			
Leu	Arg	Tyr	Gln	Thr	Asp	Ser	Gly	Cys	Trp	Tyr	Gly	Met	Glu	Ile	
	1100					1105						1110			
Arg	Pro	Gln	Arg	His	Asp	Glu	Lys	Thr	Leu	Val	Gln	Ser	Gln	Val	
	1115					1120						1125			
Asn	Ala	Tyr	Asn	Ala	Asp	Met	Ile	Asp	Pro	Phe	Gln	Leu	Gly	Leu	
	1130					1135						1140			
Leu	Val	Val	Phe	Leu	Ala	Thr	Gln	Glu	Val	Leu	Arg	Lys	Arg	Trp	
	1145					1150						1155			
Thr	Ala	Lys	Ile	Ser	Met	Pro	Ala	Ile	Leu	Ile	Ala	Leu	Leu	Val	
	1160					1165						1170			
Leu	Val	Phe	Gly	Gly	Ile	Thr	Tyr	Thr	Asp	Val	Leu	Arg	Tyr	Val	
	1175					1180						1185			
Ile	Leu	Val	Gly	Ala	Ala	Phe	Ala	Glu	Ser	Asn	Ser	Gly	Gly	Asp	
	1190					1195						1200			
Val	Val	His	Leu	Ala	Leu	Met	Ala	Thr	Phe	Lys	Ile	Gln	Pro	Val	
	1205					1210						1215			
Phe	Met	Val	Ala	Ser	Phe	Leu	Lys	Ala	Arg	Trp	Thr	Asn	Gln	Glu	
	1220					1225						1230			
Asn	Ile	Leu	Leu	Met	Leu	Ala	Ala	Val	Phe	Phe	Gln	Met	Ala	Tyr	
	1235					1240						1245			

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Tyr Asp 1250	Ala Arg Gln Ile Leu 1255	Leu Trp Glu Ile Pro 1260	Asp Val Leu
Asn Ser 1265	Leu Ala Val Ala Trp 1270	Met Ile Leu Arg Ala 1275	Ile Thr Phe
Thr Thr 1280	Thr Ser Asn Val Val 1285	Val Pro Leu Leu Ala 1290	Leu Leu Thr
Pro Gly 1295	Leu Arg Cys Leu Asn 1300	Leu Asp Val Tyr Arg 1305	Ile Leu Leu
Leu Met 1310	Val Gly Ile Gly Ser 1315	Leu Ile Arg Glu Lys 1320	Arg Ser Ala
Ala Ala 1325	Lys Lys Lys Gly Ala 1330	Ser Leu Leu Cys Leu 1335	Ala Leu Ala
Ser Thr 1340	Gly Leu Phe Asn Pro 1345	Met Ile Leu Ala Ala 1350	Gly Leu Ile
Ala Cys 1355	Asp Pro Asn Arg Lys 1360	Arg Gly Trp Pro Ala 1365	Thr Glu Val
Met Thr 1370	Ala Val Gly Leu Met 1375	Phe Ala Ile Val Gly 1380	Gly Leu Ala
Glu Leu 1385	Asp Ile Asp Ser Met 1390	Ala Ile Pro Met Thr 1395	Ile Ala Gly
Leu Met 1400	Phe Ala Ala Phe Val 1405	Ile Ser Gly Lys Ser 1410	Thr Asp Met
Trp Ile 1415	Glu Arg Thr Ala Asp 1420	Ile Ser Trp Glu Ser 1425	Asp Ala Glu
Ile Thr 1430	Gly Ser Ser Glu Arg 1435	Val Asp Val Arg Leu 1440	Asp Asp Asp
Gly Asn 1445	Phe Gln Leu Met Asn 1450	Asp Pro Gly Ala Pro 1455	Trp Lys Ile
Trp Met 1460	Leu Arg Met Val Cys 1465	Leu Ala Ile Ser Ala 1470	Tyr Thr Pro
Trp Ala 1475	Ile Leu Pro Ser Val 1480	Val Gly Phe Trp Ile 1485	Thr Leu Gln
Tyr Thr 1490	Lys Arg Gly Gly Val 1495	Leu Trp Asp Thr Pro 1500	Ser Pro Lys
Glu Tyr 1505	Lys Lys Gly Asp Thr 1510	Thr Thr Gly Val Tyr 1515	Arg Ile Met
Thr Arg 1520	Gly Leu Leu Gly Ser 1525	Tyr Gln Ala Gly Ala 1530	Gly Val Met
Val Glu 1535	Gly Val Phe His Thr 1540	Leu Trp His Thr Thr 1545	Lys Gly Ala
Ala Leu 1550	Met Ser Gly Glu Gly 1555	Arg Leu Asp Pro Tyr 1560	Trp Gly Ser
Val Lys 1565	Glu Asp Arg Leu Cys 1570	Tyr Gly Gly Pro Trp 1575	Lys Leu Gln
His Lys 1580	Trp Asn Gly Gln Asp 1585	Glu Val Gln Met Ile 1590	Val Val Glu
Pro Gly 1595	Arg Asn Val Lys Asn 1600	Val Gln Thr Lys Pro 1605	Gly Val Phe
Lys Thr 1610	Pro Glu Gly Glu Ile 1615	Gly Ala Val Thr Leu 1620	Asp Phe Pro
Thr Gly 1625	Thr Ser Gly Ser Pro 1630	Ile Val Asp Lys Asn 1635	Gly Asp Val
Ile Gly	Leu Tyr Gly Asn Gly	Val Ile Met Pro Asn	Gly Ser Tyr

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1640	1645	1650
Ile Ser Ala Ile Val Gln Gly Glu Arg Met Asp Glu Pro Ile Pro 1655 1660 1665		
Ala Gly Phe Glu Pro Glu Met Leu Arg Lys Lys Gln Ile Thr Val 1670 1675 1680		
Leu Asp Leu His Pro Gly Ala Gly Lys Thr Arg Arg Ile Leu Pro 1685 1690 1695		
Gln Ile Ile Lys Glu Ala Ile Asn Arg Arg Leu Arg Thr Ala Val 1700 1705 1710		
Leu Ala Pro Thr Arg Val Val Ala Ala Glu Met Ala Glu Ala Leu 1715 1720 1725		
Arg Gly Leu Pro Ile Arg Tyr Gln Thr Ser Ala Val Pro Arg Glu 1730 1735 1740		
His Asn Gly Asn Glu Ile Val Asp Val Met Cys His Ala Thr Leu 1745 1750 1755		
Thr His Arg Leu Met Ser Pro His Arg Val Pro Asn Tyr Asn Leu 1760 1765 1770		
Phe Val Met Asp Glu Ala His Phe Thr Asp Pro Ala Ser Ile Ala 1775 1780 1785		
Ala Arg Gly Tyr Ile Ser Thr Lys Val Glu Leu Gly Glu Ala Ala 1790 1795 1800		
Ala Ile Phe Met Thr Ala Thr Pro Pro Gly Thr Ser Asp Pro Phe 1805 1810 1815		
Pro Glu Ser Asn Ser Pro Ile Ser Asp Leu Gln Thr Glu Ile Pro 1820 1825 1830		
Asp Arg Ala Trp Asn Ser Gly Tyr Glu Trp Ile Thr Glu Tyr Thr 1835 1840 1845		
Gly Lys Thr Val Trp Phe Val Pro Ser Val Lys Met Gly Asn Glu 1850 1855 1860		
Ile Ala Leu Cys Leu Gln Arg Ala Gly Lys Lys Val Val Gln Leu 1865 1870 1875		
Asn Arg Lys Ser Tyr Glu Thr Glu Tyr Pro Lys Cys Lys Asn Asp 1880 1885 1890		
Asp Trp Asp Phe Val Ile Thr Thr Asp Ile Ser Glu Met Gly Ala 1895 1900 1905		
Asn Phe Lys Ala Ser Arg Val Ile Asp Ser Arg Lys Ser Val Lys 1910 1915 1920		
Pro Thr Ile Ile Thr Glu Gly Glu Gly Arg Val Ile Leu Gly Glu 1925 1930 1935		
Pro Ser Ala Val Thr Ala Ala Ser Ala Ala Gln Arg Arg Gly Arg 1940 1945 1950		
Ile Gly Arg Asn Pro Ser Gln Val Gly Asp Glu Tyr Cys Tyr Gly 1955 1960 1965		
Gly His Thr Asn Glu Asp Asp Ser Asn Phe Ala His Trp Thr Glu 1970 1975 1980		
Ala Arg Ile Met Leu Asp Asn Ile Asn Met Pro Asn Gly Leu Ile 1985 1990 1995		
Ala Gln Phe Tyr Gln Pro Glu Arg Glu Lys Val Tyr Thr Met Asp 2000 2005 2010		
Gly Glu Tyr Arg Leu Arg Gly Glu Glu Arg Lys Asn Phe Leu Glu 2015 2020 2025		
Leu Leu Arg Thr Ala Asp Leu Pro Val Trp Leu Ala Tyr Lys Val 2030 2035 2040		

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Ala	Ala	Ala	Gly	Val	Ser	Tyr	His	Asp	Arg	Arg	Trp	Cys	Phe	Asp
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Gly	Pro	Arg	Thr	Asn	Thr	Ile	Leu	Glu	Asp	Asn	Asn	Glu	Val	Glu
	2060					2065					2070			
Val	Ile	Thr	Lys	Leu	Gly	Glu	Arg	Lys	Ile	Leu	Arg	Pro	Arg	Trp
	2075					2080					2085			
Ile	Asp	Ala	Arg	Val	Tyr	Ser	Asp	His	Gln	Ala	Leu	Lys	Ala	Phe
	2090					2095					2100			
Lys	Asp	Phe	Ala	Ser	Gly	Lys	Arg	Ser	Gln	Ile	Gly	Leu	Ile	Glu
	2105					2110					2115			
Val	Leu	Gly	Lys	Met	Pro	Glu	His	Phe	Met	Gly	Lys	Thr	Trp	Glu
	2120					2125					2130			
Ala	Leu	Asp	Thr	Met	Tyr	Val	Val	Ala	Thr	Ala	Glu	Lys	Gly	Gly
	2135					2140					2145			
Arg	Ala	His	Arg	Met	Ala	Leu	Glu	Glu	Leu	Pro	Asp	Ala	Leu	Gln
	2150					2155					2160			
Thr	Ile	Ala	Leu	Ile	Ala	Leu	Leu	Ser	Val	Met	Thr	Met	Gly	Val
	2165					2170					2175			
Phe	Phe	Leu	Leu	Met	Gln	Arg	Lys	Gly	Ile	Gly	Lys	Ile	Gly	Leu
	2180					2185					2190			
Gly	Gly	Ala	Val	Leu	Gly	Val	Ala	Thr	Phe	Phe	Cys	Trp	Met	Ala
	2195					2200					2205			
Glu	Val	Pro	Gly	Thr	Lys	Ile	Ala	Gly	Met	Leu	Leu	Leu	Ser	Leu
	2210					2215					2220			
Leu	Leu	Met	Ile	Val	Leu	Ile	Pro	Glu	Pro	Glu	Lys	Gln	Arg	Ser
	2225					2230					2235			
Gln	Thr	Asp	Asn	Gln	Leu	Ala	Val	Phe	Leu	Ile	Cys	Val	Met	Thr
	2240					2245					2250			
Leu	Val	Ser	Ala	Val	Ala	Ala	Asn	Glu	Met	Gly	Trp	Leu	Asp	Lys
	2255					2260					2265			
Thr	Lys	Ser	Asp	Ile	Ser	Ser	Leu	Phe	Gly	Gln	Arg	Ile	Glu	Val
	2270					2275					2280			
Lys	Glu	Asn	Phe	Ser	Met	Gly	Glu	Phe	Leu	Leu	Asp	Leu	Arg	Pro
	2285					2290					2295			
Ala	Thr	Ala	Trp	Ser	Leu	Tyr	Ala	Val	Thr	Thr	Ala	Val	Leu	Thr
	2300					2305					2310			
Pro	Leu	Leu	Lys	His	Leu	Ile	Thr	Ser	Asp	Tyr	Ile	Asn	Thr	Ser
	2315					2320					2325			
Leu	Thr	Ser	Ile	Asn	Val	Gln	Ala	Ser	Ala	Leu	Phe	Thr	Leu	Ala
	2330					2335					2340			
Arg	Gly	Phe	Pro	Phe	Val	Asp	Val	Gly	Val	Ser	Ala	Leu	Leu	Leu
	2345					2350					2355			
Ala	Ala	Gly	Cys	Trp	Gly	Gln	Val	Thr	Leu	Thr	Val	Thr	Val	Thr
	2360					2365					2370			
Ala	Ala	Thr	Leu	Leu	Phe	Cys	His	Tyr	Ala	Tyr	Met	Val	Pro	Gly
	2375					2380					2385			
Trp	Gln	Ala	Glu	Ala	Met	Arg	Ser	Ala	Gln	Arg	Arg	Thr	Ala	Ala
	2390					2395					2400			
Gly	Ile	Met	Lys	Asn	Ala	Val	Val	Asp	Gly	Ile	Val	Ala	Thr	Asp
	2405					2410					2415			
Val	Pro	Glu	Leu	Glu	Arg	Thr	Thr	Pro	Ile	Met	Gln	Lys	Lys	Val
	2420					2425					2430			
Gly	Gln	Ile	Met	Leu	Ile	Leu	Val	Ser	Leu	Ala	Ala	Val	Val	Val
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Asn Pro 2450	Ser Val Lys Thr Val 2455	Arg Glu Ala Gly Ile 2460	Leu Ile Thr
Ala Ala 2465	Ala Val Thr Leu Trp 2470	Glu Asn Gly Ala Ser 2475	Ser Val Trp
Asn Ala 2480	Thr Thr Ala Ile Gly 2485	Leu Cys His Ile Met 2490	Arg Gly Gly
Trp Leu 2495	Ser Cys Leu Ser Ile 2500	Thr Trp Thr Leu Ile 2505	Lys Asn Met
Glu Lys 2510	Pro Gly Leu Lys Arg 2515	Gly Gly Ala Lys Gly 2520	Arg Thr Leu
Gly Glu 2525	Val Trp Lys Glu Arg 2530	Leu Asn Gln Met Thr 2535	Lys Glu Glu
Phe Thr 2540	Arg Tyr Arg Lys Glu 2545	Ala Ile Ile Glu Val 2550	Asp Arg Ser
Ala Ala 2555	Lys His Ala Arg Lys 2560	Glu Gly Asn Val Thr 2565	Gly Gly His
Pro Val 2570	Ser Arg Gly Thr Ala 2575	Lys Leu Arg Trp Leu 2580	Val Glu Arg
Arg Phe 2585	Leu Glu Pro Val Gly 2590	Lys Val Ile Asp Leu 2595	Gly Cys Gly
Arg Gly 2600	Gly Trp Cys Tyr Tyr 2605	Met Ala Thr Gln Lys 2610	Arg Val Gln
Glu Val 2615	Arg Gly Tyr Thr Lys 2620	Gly Gly Pro Gly His 2625	Glu Glu Pro
Gln Leu 2630	Val Gln Ser Tyr Gly 2635	Trp Asn Ile Val Thr 2640	Met Lys Ser
Gly Val 2645	Asp Val Phe Tyr Arg 2650	Pro Ser Glu Cys Cys 2655	Asp Thr Leu
Leu Cys 2660	Asp Ile Gly Glu Ser 2665	Ser Ser Ser Ala Glu 2670	Val Glu Glu
His Arg 2675	Thr Ile Arg Val Leu 2680	Glu Met Val Glu Asp 2685	Trp Leu His
Arg Gly 2690	Pro Arg Glu Phe Cys 2695	Val Lys Val Leu Cys 2700	Pro Tyr Met
Pro Lys 2705	Val Ile Glu Lys Met 2710	Glu Leu Leu Gln Arg 2715	Arg Tyr Gly
Gly Gly 2720	Leu Val Arg Asn Pro 2725	Leu Ser Arg Asn Ser 2730	Thr His Glu
Met Tyr 2735	Trp Val Ser Arg Ala 2740	Ser Gly Asn Val Val 2745	His Ser Val
Asn Met 2750	Thr Ser Gln Val Leu 2755	Leu Gly Arg Met Glu 2760	Lys Arg Thr
Trp Lys 2765	Gly Pro Gln Tyr Glu 2770	Glu Asp Val Asn Leu 2775	Gly Ser Gly
Thr Arg 2780	Ala Val Gly Lys Pro 2785	Leu Leu Asn Ser Asp 2790	Thr Ser Lys
Ile Lys 2795	Asn Arg Ile Glu Arg 2800	Leu Arg Arg Glu Tyr 2805	Ser Ser Thr
Trp His 2810	His Asp Glu Asn His 2815	Pro Tyr Arg Thr Trp 2820	Asn Tyr His
Gly Ser 2825	Tyr Asp Val Lys Pro 2830	Thr Gly Ser Ala Ser 2835	Ser Leu Val
Asn Gly	Val Val Arg Leu Leu	Ser Lys Pro Trp Asp	Thr Ile Thr

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2840	2845	2850
Asn Val Thr Thr Met Ala Met Thr Asp Thr Thr Pro Phe Gly Gln 2855 2860 2865		
Gln Arg Val Phe Lys Glu Lys Val Asp Thr Lys Ala Pro Glu Pro 2870 2875 2880		
Pro Glu Gly Val Lys Tyr Val Leu Asn Glu Thr Thr Asn Trp Leu 2885 2890 2895		
Trp Ala Phe Leu Ala Arg Glu Lys Arg Pro Arg Met Cys Ser Arg 2900 2905 2910		
Glu Glu Phe Ile Arg Lys Val Asn Ser Asn Ala Ala Leu Gly Ala 2915 2920 2925		
Met Phe Glu Glu Gln Asn Gln Trp Arg Ser Ala Arg Glu Ala Val 2930 2935 2940		
Glu Asp Pro Lys Phe Trp Glu Met Val Asp Glu Glu Arg Glu Ala 2945 2950 2955		
His Leu Arg Gly Glu Cys His Thr Cys Ile Tyr Asn Met Met Gly 2960 2965 2970		
Lys Arg Glu Lys Lys Pro Gly Glu Phe Gly Lys Ala Lys Gly Ser 2975 2980 2985		
Arg Ala Ile Trp Phe Met Trp Leu Gly Ala Arg Phe Leu Glu Phe 2990 2995 3000		
Glu Ala Leu Gly Phe Leu Asn Glu Asp His Trp Leu Gly Arg Lys 3005 3010 3015		
Asn Ser Gly Gly Gly Val Glu Gly Leu Gly Leu Gln Lys Leu Gly 3020 3025 3030		
Tyr Ile Leu Arg Glu Val Gly Thr Arg Pro Gly Gly Lys Ile Tyr 3035 3040 3045		
Ala Asp Asp Thr Ala Gly Trp Asp Thr Arg Ile Thr Arg Ala Asp 3050 3055 3060		
Leu Glu Asn Glu Ala Lys Val Leu Glu Leu Leu Asp Gly Glu His 3065 3070 3075		
Arg Arg Leu Ala Arg Ala Ile Ile Glu Leu Thr Tyr Arg His Lys 3080 3085 3090		
Val Val Lys Val Met Arg Pro Ala Ala Asp Gly Arg Thr Val Met 3095 3100 3105		
Asp Val Ile Ser Arg Glu Asp Gln Arg Gly Ser Gly Gln Val Val 3110 3115 3120		
Thr Tyr Ala Leu Asn Thr Phe Thr Asn Leu Ala Val Gln Leu Val 3125 3130 3135		
Arg Met Met Glu Gly Glu Gly Val Ile Gly Pro Asp Asp Val Glu 3140 3145 3150		
Lys Leu Thr Lys Gly Lys Gly Pro Lys Val Arg Thr Trp Leu Phe 3155 3160 3165		
Glu Asn Gly Glu Glu Arg Leu Ser Arg Met Ala Val Ser Gly Asp 3170 3175 3180		
Asp Cys Val Val Lys Pro Leu Asp Asp Arg Phe Ala Thr Ser Leu 3185 3190 3195		
His Phe Leu Asn Ala Met Ser Lys Val Arg Lys Asp Ile Gln Glu 3200 3205 3210		
Trp Lys Pro Ser Thr Gly Trp Tyr Asp Trp Gln Gln Val Pro Phe 3215 3220 3225		
Cys Ser Asn His Phe Thr Glu Leu Ile Met Lys Asp Gly Arg Thr 3230 3235 3240		

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Leu Val	Val Pro Cys Arg Gly	Gln Asp Glu Leu Val	Gly Arg Ala
3245	3250	3255	
Arg Ile	Ser Pro Gly Ala Gly	Trp Asn Val Arg Asp	Thr Ala Cys
3260	3265	3270	
Leu Ala	Lys Ser Tyr Ala Gln	Met Trp Leu Leu Leu	Tyr Phe His
3275	3280	3285	
Arg Arg	Asp Leu Arg Leu Met	Ala Asn Ala Ile Cys	Ser Ala Val
3290	3295	3300	
Pro Val	Asn Trp Val Pro Thr	Gly Arg Thr Thr Trp	Ser Ile His
3305	3310	3315	
Ala Gly	Gly Glu Trp Met Thr	Thr Glu Asp Met Leu	Glu Val Trp
3320	3325	3330	
Asn Arg	Val Trp Ile Glu Glu	Asn Glu Trp Met Glu	Asp Lys Thr
3335	3340	3345	
Pro Val	Glu Lys Trp Ser Asp	Val Pro Tyr Ser Gly	Lys Arg Glu
3350	3355	3360	
Asp Ile	Trp Cys Gly Ser Leu	Ile Gly Thr Arg Ala	Arg Ala Thr
3365	3370	3375	
Trp Ala	Glu Asn Ile Gln Val	Ala Ile Asn Gln Val	Arg Ala Ile
3380	3385	3390	
Ile Gly	Asp Glu Lys Tyr Val	Asp Tyr Met Ser Ser	Leu Lys Arg
3395	3400	3405	
Tyr Glu	Asp Thr Thr Leu Val	Glu Asp Thr Val Leu	
3410	3415	3420	

<210> SEQ ID NO 7

<211> LENGTH: 10996

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Recombinant West Nile virus/Dengue-4 virus chimera

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (97)..(10362)

<400> SEQUENCE: 7

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Met Ser Lys Lys Pro Gly	
1 5	
ggg ccc ggc aag agc cgg gct gtc aat atg cta aaa cgc gga atg ccc	162
Gly Pro Gly Lys Ser Arg Ala Val Asn Met Leu Lys Arg Gly Met Pro	
10 15 20	
cgc gtg ttg tcc ttg att gga ctg aag agg gct atg ttg agc ctg atc	210
Arg Val Leu Ser Leu Ile Gly Leu Lys Arg Ala Met Leu Ser Leu Ile	
25 30 35	
gac ggc aag ggg cca ata cga ttt gtg ttg gct ctc ttg gcg ttc ttc	258
Asp Gly Lys Gly Pro Ile Arg Phe Val Leu Ala Leu Leu Ala Phe Phe	
40 45 50	
agg ttc aca gca att gct ccg acc cga gca gtg ctg gat cga tgg aga	306
Arg Phe Thr Ala Ile Ala Pro Thr Arg Ala Val Leu Asp Arg Trp Arg	
55 60 65 70	
ggt gtg aac aaa caa aca gcg atg aaa cac ctt ctg agt ttt aag aag	354
Gly Val Asn Lys Gln Thr Ala Met Lys His Leu Leu Ser Phe Lys Lys	
75 80 85	
gaa cta ggg acc ttg acc agt gct atc aat cgg cgg agc tca aaa caa	402
Glu Leu Gly Thr Leu Thr Ser Ala Ile Asn Arg Arg Ser Ser Lys Gln	
90 95 100	

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aag aaa aga tca acg ata aca ttg ctg tgc ttg att ccc acc gta atg	450
Lys Lys Arg Ser Thr Ile Thr Leu Leu Cys Leu Ile Pro Thr Val Met	
105 110 115	
gcg ttt cac ttg tca aca aga gat gcc gaa ccc ctc atg ata gtg gca	498
Ala Phe His Leu Ser Thr Arg Asp Gly Glu Pro Leu Met Ile Val Ala	
120 125 130	
aaa cat gaa agg ggg aga cct ctc ctg ttt aag aca aca gag ggg atc	546
Lys His Glu Arg Gly Arg Pro Leu Leu Phe Lys Thr Thr Glu Gly Ile	
135 140 145 150	
aac aaa tgc act ctc att gcc atg gac ttg ggt gaa atg tgt gag gac	594
Asn Lys Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Met Cys Glu Asp	
155 160 165	
act gtc acg tac aaa tgc ccc tta ctg gtc aat acc gaa cct gaa gac	642
Thr Val Thr Tyr Lys Cys Pro Leu Leu Val Asn Thr Glu Pro Glu Asp	
170 175 180	
att gat tgc tgg tgc aat ctc acg tct acc tgg gtc atg tat ggg aca	690
Ile Asp Cys Trp Cys Asn Leu Thr Ser Thr Trp Val Met Tyr Gly Thr	
185 190 195	
tgc acc cag agc gga gaa cgg aga cga gag aag cgc tca gta gct tta	738
Cys Thr Gln Ser Gly Glu Arg Arg Arg Glu Lys Arg Ser Val Ala Leu	
200 205 210	
aca cca cat tca gga atg gga ttg gaa aca aga gct gag aca tgg atg	786
Thr Pro His Ser Gly Met Gly Leu Glu Thr Arg Ala Glu Thr Trp Met	
215 220 225 230	
tca tcg gaa ggg gct tgg aag cat gct cag aga gta gag agc tgg ata	834
Ser Ser Glu Gly Ala Trp Lys His Ala Gln Arg Val Glu Ser Trp Ile	
235 240 245	
ctc aga aac cca gga ttc gcg ctc ttg gca gga ttt atg gct tat atg	882
Leu Arg Asn Pro Gly Phe Ala Leu Leu Ala Gly Phe Met Ala Tyr Met	
250 255 260	
att ggg caa aca gga atc cag cga act gtc ttc ttt gtc cta atg atg	930
Ile Gly Gln Thr Gly Ile Gln Arg Thr Val Phe Phe Val Leu Met Met	
265 270 275	
ctg gtc gcc cca tcc tac gga atg cga tgc gta gga gta ggg aac aga	978
Leu Val Ala Pro Ser Tyr Gly Met Arg Cys Val Gly Val Gly Asn Arg	
280 285 290	
gac ttt gtg gaa gga gtc tca ggt gga gca tgg gtc gat ctg gtg cta	1026
Asp Phe Val Glu Gly Val Ser Gly Gly Ala Trp Val Asp Leu Val Leu	
295 300 305 310	
gaa cat gga gga tgc gtc aca acc atg gcc cag gga aaa cca acc ttg	1074
Glu His Gly Gly Cys Val Thr Thr Met Ala Gln Gly Lys Pro Thr Leu	
315 320 325	
gat ttt gaa ctg act aag aca aca gcc aag gaa gtg gct ctg tta aga	1122
Asp Phe Glu Leu Thr Lys Thr Thr Ala Lys Glu Val Ala Leu Leu Arg	
330 335 340	
acc tat tgc att gaa gcc tca ata tca aac ata acc acg gca aca aga	1170
Thr Tyr Cys Ile Glu Ala Ser Ile Ser Asn Ile Thr Thr Ala Thr Arg	
345 350 355	
tgt cca acg caa gga gag cct tat cta aaa gag gaa caa gac caa cag	1218
Cys Pro Thr Gln Gly Glu Pro Tyr Leu Lys Glu Glu Gln Asp Gln Gln	
360 365 370	
tac att tgc cgg aga gat gtg gta gac aga ggg tgg ggc aat ggc tgt	1266
Tyr Ile Cys Arg Arg Asp Val Val Asp Arg Gly Trp Gly Asn Gly Cys	
375 380 385 390	
ggc ttg ttt gga aaa gga gga gtt gtg aca tgt gcg aag ttt tca tgt	1314
Gly Leu Phe Gly Lys Gly Gly Val Val Thr Cys Ala Lys Phe Ser Cys	
395 400 405	
tcg ggg aag ata aca ggc aat ttg gtc caa att gag aac ctt gaa tac	1362
Ser Gly Lys Ile Thr Gly Asn Leu Val Gln Ile Glu Asn Leu Glu Tyr	
410 415 420	

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aca gtt gtt gta aca gtc cac aat gga gac acc cat gca gta gga aat	1410
Thr Val Val Val Thr Val His Asn Gly Asp Thr His Ala Val Gly Asn	
425 430 435	
gac aca tcc aat cat gga gtt aca gcc acg ata act ccc agg tca cca	1458
Asp Thr Ser Asn His Gly Val Thr Ala Thr Ile Thr Pro Arg Ser Pro	
440 445 450	
tcg gtg gaa gtc aaa ttg ccg gac tat gga gaa cta aca ctc gat tgt	1506
Ser Val Glu Val Lys Leu Pro Asp Tyr Gly Glu Leu Thr Leu Asp Cys	
455 460 465 470	
gaa ccc agg tct gga att gac ttt aat gag atg att ctg atg aaa atg	1554
Glu Pro Arg Ser Gly Ile Asp Phe Asn Glu Met Ile Leu Met Lys Met	
475 480 485	
aaa aag aaa aca tgg ctt gtg cat aag caa tgg ttt ttg gat cta cct	1602
Lys Lys Lys Thr Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu Pro	
490 495 500	
cta cca tgg aca gca gga gca gac aca tca gag gtt cac tgg aat tac	1650
Leu Pro Trp Thr Ala Gly Ala Asp Thr Ser Glu Val His Trp Asn Tyr	
505 510 515	
aaa gag aga atg gtg aca ttt aag gtt cct cat gcc aag aga cag gat	1698
Lys Glu Arg Met Val Thr Phe Lys Val Pro His Ala Lys Arg Gln Asp	
520 525 530	
gtg aca gtg ctg gga tct cag gaa gga gcc atg cat tct gcc ctc gct	1746
Val Thr Val Leu Gly Ser Gln Glu Gly Ala Met His Ser Ala Leu Ala	
535 540 545 550	
gga gcc aca gaa gtg gac tcc ggt gat gga aat cac atg ttt gca gga	1794
Gly Ala Thr Glu Val Asp Ser Gly Asp Gly Asn His Met Phe Ala Gly	
555 560 565	
cat ctc aag tgc aaa gtc cgt atg gag aaa ttg aga atc aag gga atg	1842
His Leu Lys Cys Lys Val Arg Met Glu Lys Leu Arg Ile Lys Gly Met	
570 575 580	
tca tac acg atg tgt tca gga aag ttc tca att gac aaa gag atg gca	1890
Ser Tyr Thr Met Cys Ser Gly Lys Phe Ser Ile Asp Lys Glu Met Ala	
585 590 595	
gaa aca cag cat ggg aca aca gtg gtg aaa gtc aag tat gaa ggt gct	1938
Glu Thr Gln His Gly Thr Thr Val Val Lys Val Lys Tyr Glu Gly Ala	
600 605 610	
gga gct ccg tgt aaa gtc ccc ata gag ata aga gat gtg aac aag gaa	1986
Gly Ala Pro Cys Lys Val Pro Ile Glu Ile Arg Asp Val Asn Lys Glu	
615 620 625 630	
aaa gtg gtt ggg cgt atc atc tca tcc acc cct ttg gct gag aat acc	2034
Lys Val Val Gly Arg Ile Ile Ser Ser Thr Pro Leu Ala Glu Asn Thr	
635 640 645	
aac agt gca acc aac ata gag tta gaa ccc ccc ttt ggg gac agc tac	2082
Asn Ser Ala Thr Asn Ile Glu Leu Glu Pro Pro Phe Gly Asp Ser Tyr	
650 655 660	
ata gtg ata ggt gtt gga aac agt gca tta aca ctc cat tgg ttc agg	2130
Ile Val Ile Gly Val Gly Asn Ser Ala Leu Thr Leu His Trp Phe Arg	
665 670 675	
aaa ggg agt tcc att ggc aag atg ttt gag tcc aca tac aga ggt gca	2178
Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ser Thr Tyr Arg Gly Ala	
680 685 690	
aaa cga atg gcc att cta ggt gaa aca gct tgg gat ttt ggt tcc gtt	2226
Lys Arg Met Ala Ile Leu Gly Glu Thr Ala Trp Asp Phe Gly Ser Val	
695 700 705 710	
ggt gga ctg ttc aca tca ttg gga aag gct gtg cac cag gtt ttt gga	2274
Gly Gly Leu Phe Thr Ser Leu Gly Lys Ala Val His Gln Val Phe Gly	
715 720 725	
agt gtg tat aca acc atg ttt gga gga gtc tca tgg atg att aga atc	2322
Ser Val Tyr Thr Thr Met Phe Gly Gly Val Ser Trp Met Ile Arg Ile	
730 735 740	

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cta att ggg ttc cta gtg ttg tgg att ggc acg aac tca agg aac act Leu Ile Gly Phe Leu Val Leu Trp Ile Gly Thr Asn Ser Arg Asn Thr 745 750 755	2370
tca atg gct atg acg tgc ata gct gtt gga gga atc act ctg ttt ctg Ser Met Ala Met Thr Cys Ile Ala Val Gly Gly Ile Thr Leu Phe Leu 760 765 770	2418
ggc ttc aca gtt caa gca gac tcc gga tgt gcc ata gac atc agc cgg Gly Phe Thr Val Gln Ala Asp Ser Gly Cys Ala Ile Asp Ile Ser Arg 775 780 785 790	2466
caa gag ctg aga tgt gga agt gga gtg ttc ata cac aat gat gtg gag Gln Glu Leu Arg Cys Gly Ser Gly Val Phe Ile His Asn Asp Val Glu 795 800 805	2514
gct tgg atg gac cgg tac aag tat tac cct gaa acg cca caa ggc cta Ala Trp Met Asp Arg Tyr Lys Tyr Pro Glu Thr Pro Gln Gly Leu 810 815 820	2562
gcc aag atc att cag aaa gct cat aag gaa gga gtg tgc ggt cta cga Ala Lys Ile Ile Gln Lys Ala His Lys Glu Gly Val Cys Gly Leu Arg 825 830 835	2610
tca gtt tcc aga ctg gag cat caa atg tgg gaa gca gtg aag gac gag Ser Val Ser Arg Leu Glu His Gln Met Trp Glu Ala Val Lys Asp Glu 840 845 850	2658
ctg aac act ctt ttg aag gag aat ggt gtg gac ctt agt gtc gtg gtt Leu Asn Thr Leu Leu Lys Glu Asn Gly Val Asp Leu Ser Val Val Val 855 860 865 870	2706
gag aaa cag gag gga atg tac aag tca gca cct aaa cgc ctc acc gcc Glu Lys Gln Glu Gly Met Tyr Lys Ser Ala Pro Lys Arg Leu Thr Ala 875 880 885	2754
acc acg gaa aaa ttg gaa att ggc tgg aag gcc tgg gga aag agt att Thr Thr Glu Lys Leu Glu Ile Gly Trp Lys Ala Trp Gly Lys Ser Ile 890 895 900	2802
tta ttt gca cca gaa ctc gcc aac aac acc ttt gtg gtt gat ggt ccg Leu Phe Ala Pro Glu Leu Ala Asn Asn Thr Phe Val Val Asp Gly Pro 905 910 915	2850
gag acc aag gaa tgt ccg act cag aat cgc gct tgg aat agc tta gaa Glu Thr Lys Glu Cys Pro Thr Gln Asn Arg Ala Trp Asn Ser Leu Glu 920 925 930	2898
gtg gag gat ttt gga ttt ggt ctc acc agc act cgg atg ttc ctg aag Val Glu Asp Phe Gly Phe Gly Leu Thr Ser Thr Arg Met Phe Leu Lys 935 940 945 950	2946
gtc aga gag agc aac aca act gaa tgt gac tcg aag atc att gga acg Val Arg Glu Ser Asn Thr Thr Glu Cys Asp Ser Lys Ile Ile Gly Thr 955 960 965	2994
gct gtc aag aac aac ttg gcg atc cac agt gac ctg tcc tat tgg att Ala Val Lys Asn Asn Leu Ala Ile His Ser Asp Leu Ser Tyr Trp Ile 970 975 980	3042
gaa agc agg ctc aat gat acg tgg aag ctt gaa agg gca gtt ctg ggt Glu Ser Arg Leu Asn Asp Thr Trp Lys Leu Glu Arg Ala Val Leu Gly 985 990 995	3090
gaa gtc aaa tca tgt acg tgg cct gag acg cat acc ttg tgg ggc Glu Val Lys Ser Cys Thr Trp Pro Glu Thr His Thr Leu Trp Gly 1000 1005 1010	3135
gat gga atc ctt gag agt gac ttg ata ata cca gtc aca ctg gcg Asp Gly Ile Leu Glu Ser Asp Leu Ile Ile Pro Val Thr Leu Ala 1015 1020 1025	3180
gga cca cga agc aat cac aat cgg aga cct ggg tac aag aca caa Gly Pro Arg Ser Asn His Asn Arg Arg Pro Gly Tyr Lys Thr Gln 1030 1035 1040	3225
aac cag ggc cca tgg gac gaa ggc cgg gta gag att gac ttc gat Asn Gln Gly Pro Trp Asp Glu Gly Arg Val Glu Ile Asp Phe Asp 1045 1050 1055	3270

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tac tgc	cca gga act acg gtc	acc ctg agt gag agc	tgc gga cac	3315
Tyr Cys	Pro Gly Thr Thr Val	Thr Leu Ser Glu Ser	Cys Gly His	
1060	1065	1070		
cgt gga	cct gcc act cgc acc	acc aca gag agc gga	aag ttg ata	3360
Arg Gly	Pro Ala Thr Arg Thr	Thr Thr Glu Ser Gly	Lys Leu Ile	
1075	1080	1085		
aca gat	tgg tgc tgc agg agc	tgc acc tta cca cca	ctg cgc tac	3405
Thr Asp	Trp Cys Cys Arg Ser	Cys Thr Leu Pro Pro	Leu Arg Tyr	
1090	1095	1100		
caa act	gac agc ggc tgt tgg	tat ggt atg gag atc	aga cca cag	3450
Gln Thr	Asp Ser Gly Cys Trp	Tyr Gly Met Glu Ile	Arg Pro Gln	
1105	1110	1115		
aga cat	gat gaa aag acc ctc	gtg cag tca caa gtg	aat gct tat	3495
Arg His	Asp Glu Lys Thr Leu	Val Gln Ser Gln Val	Asn Ala Tyr	
1120	1125	1130		
aat gct	gat atg att gac cct	ttt cag ttg ggc ctt	ctg gtc gtg	3540
Asn Ala	Asp Met Ile Asp Pro	Phe Gln Leu Gly Leu	Leu Val Val	
1135	1140	1145		
ttc ttg	gcc acc cag gag gtc	ctt cgc aag agg tgg	aca gcc aag	3585
Phe Leu	Ala Thr Gln Glu Val	Leu Arg Lys Arg Trp	Thr Ala Lys	
1150	1155	1160		
atc agc	atg cca gct ata ctg	att gct ctg cta gtc	ctg gtg ttt	3630
Ile Ser	Met Pro Ala Ile Leu	Ile Ala Leu Leu Val	Leu Val Phe	
1165	1170	1175		
ggg ggc	att act tac act gat	gtg tta cgc tat gtc	atc ttg gtg	3675
Gly Gly	Ile Thr Tyr Thr Asp	Val Leu Arg Tyr Val	Ile Leu Val	
1180	1185	1190		
ggg gca	gct ttc gca gaa tct	aat tcg gga gga gac	gtg gta cac	3720
Gly Ala	Ala Phe Ala Glu Ser	Asn Ser Gly Gly Asp	Val Val His	
1195	1200	1205		
ttg gcg	ctc atg gcg acc ttc	aag ata caa cca gtg	ttt atg gtg	3765
Leu Ala	Leu Met Ala Thr Phe	Lys Ile Gln Pro Val	Phe Met Val	
1210	1215	1220		
gca tcg	ttt ctc aaa gcg aga	tgg acc aac cag gag	aac att ttg	3810
Ala Ser	Phe Leu Lys Ala Arg	Trp Thr Asn Gln Glu	Asn Ile Leu	
1225	1230	1235		
ttg atg	ttg gcg gct gtt ttc	ttt caa atg gct tat	tac gat gcc	3855
Leu Met	Leu Ala Ala Val Phe	Phe Gln Met Ala Tyr	Tyr Asp Ala	
1240	1245	1250		
cgc caa	att ctg ctc tgg gag	atc cct gat gtg ttg	aat tca ctg	3900
Arg Gln	Ile Leu Leu Trp Glu	Ile Pro Asp Val Leu	Asn Ser Leu	
1255	1260	1265		
gcg gta	gct tgg atg ata ctg	aga gcc ata aca ttc	aca acg aca	3945
Ala Val	Ala Trp Met Ile Leu	Arg Ala Ile Thr Phe	Thr Thr Thr	
1270	1275	1280		
tca aac	gtg gtt gtt ccg ctg	cta gcc ctg cta aca	ccc ggg ctg	3990
Ser Asn	Val Val Val Pro Leu	Leu Ala Leu Leu Thr	Pro Gly Leu	
1285	1290	1295		
aga tgc	ttg aat ctg gat gtg	tac agg ata ctg ctg	ttg atg gtc	4035
Arg Cys	Leu Asn Leu Asp Val	Tyr Arg Ile Leu Leu	Leu Met Val	
1300	1305	1310		
gga ata	ggc agc ttg atc agg	gag aag agg agt gca	gct gca aaa	4080
Gly Ile	Gly Ser Leu Ile Arg	Glu Lys Arg Ser Ala	Ala Ala Lys	
1315	1320	1325		
aag aaa	gga gca agt ctg cta	tgc ttg gct cta gcc	tca aca gga	4125
Lys Lys	Gly Ala Ser Leu Leu	Cys Leu Ala Leu Ala	Ser Thr Gly	
1330	1335	1340		
ctt ttc	aac ccc atg atc ctt	gct gct gga ctg att	gca tgt gat	4170
Leu Phe	Asn Pro Met Ile Leu	Ala Ala Gly Leu Ile	Ala Cys Asp	
1345	1350	1355		

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ccc aac Pro Asn 1360	cgt aaa cgc gga Arg Lys Arg Gly 1365	tgg Trp 1365	ccc gca act gaa Pro Ala Thr Glu 1370	gtg Val 1370	atg aca gct Met Thr Ala 1370	4215
gtc ggc Val Gly 1375	cta atg ttt gcc Leu Met Phe Ala 1380	atc Ile 1380	gtc gga ggg ctg Val Gly Gly Leu 1385	gca Ala 1385	gag ctt gac Glu Leu Asp 1385	4260
att gac Ile Asp 1390	tcc atg gcc att Ser Met Ala Ile 1395	cca Pro 1395	atg act atc gcg Met Thr Ile Ala 1400	ggg Gly 1400	ctc atg ttt Leu Met Phe 1400	4305
gct gct Ala Ala 1405	ttc gtg att tct Phe Val Ile Ser 1410	ggg Gly 1410	aaa tca aca gat Lys Ser Thr Asp 1415	atg Met 1415	tgg att gag Trp Ile Glu 1415	4350
aga acg Arg Thr 1420	gcg gac att tcc Ala Asp Ile Ser 1425	tgg Trp 1425	gaa agt gat gca Glu Ser Asp Ala 1430	gaa Glu 1430	att aca ggc Ile Thr Gly 1430	4395
tcg agc Ser Ser 1435	gaa aga gtt gat Glu Arg Val Asp 1440	gtg Val 1440	cgg ctt gat gat Arg Leu Asp Asp 1445	gat Asp 1445	gga aac ttc Gly Asn Phe 1445	4440
cag ctc Gln Leu 1450	atg aat gat cca Met Asn Asp Pro 1455	gga Gly 1455	gca cct tgg aag Ala Pro Trp Lys 1460	ata Ile 1460	tgg atg ctc Trp Met Leu 1460	4485
aga atg Arg Met 1465	gtc tgt ctc gcg Val Cys Leu Ala 1470	att Ile 1470	agt gcg tac acc Ser Ala Tyr Thr 1475	ccc Pro 1475	tgg gca atc Trp Ala Ile 1475	4530
ttg ccc Leu Pro 1480	tca gta gtt gga Ser Val Val Gly 1485	ttt Phe 1485	tgg ata act ctc Trp Ile Thr Leu 1490	caa Gln 1490	tac aca aag Tyr Thr Lys 1490	4575
aga gga Arg Gly 1495	ggc gtg ttg tgg Gly Val Leu Trp 1500	gac Asp 1500	act ccc tca cca Thr Pro Ser Pro 1505	aag Lys 1505	gag tac aaa Glu Tyr Lys 1505	4620
aag ggg Lys Gly 1510	gac acg acc acc Asp Thr Thr Thr 1515	ggc Gly 1515	gtc tac agg atc Val Tyr Arg Ile 1520	atg Met 1520	act cgt ggg Thr Arg Gly 1520	4665
ctg ctc Leu Leu 1525	ggc agt tat caa Gly Ser Tyr Gln 1530	gca Ala 1530	gga gcg ggc gtg Gly Ala Gly Val 1535	atg Met 1535	gtt gaa ggt Val Glu Gly 1535	4710
gtt ttc Val Phe 1540	cac acc ctt tgg His Thr Leu Trp 1545	cat His 1545	aca aca aaa gga Thr Thr Lys Gly 1550	gcc Ala 1550	gct ttg atg Ala Leu Met 1550	4755
agc gga Ser Gly 1555	gag ggc cgc ctg Glu Gly Arg Leu 1560	gac Asp 1560	cca tac tgg ggc Pro Tyr Trp Gly 1565	agt Ser 1565	gtc aag gag Val Lys Glu 1565	4800
gat cga Asp Arg 1570	ctt tgt tac gga Leu Cys Tyr Gly 1575	gga Gly 1575	ccc tgg aaa ttg Pro Trp Lys Leu 1580	cag Gln 1580	cac aag tgg His Lys Trp 1580	4845
aac ggg Asn Gly 1585	cag gat gag gtg Gln Asp Glu Val 1590	cag Gln 1590	atg att gtg gtg Met Ile Val Val 1595	gaa Glu 1595	cct ggc agg Pro Gly Arg 1595	4890
aac gtt Asn Val 1600	aag aac gtc cag Lys Asn Val Gln 1605	acg Thr 1605	aaa cca ggg gtg Lys Pro Gly Val 1610	ttc Phe 1610	aaa aca cct Lys Thr Pro 1610	4935
gaa gga Glu Gly 1615	gaa atc ggg gcc Glu Ile Gly Ala 1620	gtg Val 1620	act ttg gac ttc Thr Leu Asp Phe 1625	ccc Pro 1625	act gga aca Thr Gly Thr 1625	4980
tca ggc Ser Gly 1630	tca cca ata gtg Ser Pro Ile Val 1635	gac Asp 1635	aaa aac ggt gat Lys Asn Gly Asp 1640	gtg Val 1640	att ggg ctt Ile Gly Leu 1640	5025
tat ggc Tyr Gly 1645	aat gga gtc ata Asn Gly Val Ile 1650	atg Met 1650	ccc aac ggc tca Pro Asn Gly Ser 1655	tac Tyr 1655	ata agc gcg Ile Ser Ala 1655	5070

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ata ggt	cag ggt	gaa agg	atg	gat gag	cca atc	cca gcc	gga ttc	5115
Ile Val	Gln Gly	Glu Arg	Met	Asp Glu	Pro Ile	Pro Ala	Gly Phe	
1660			1665			1670		
gaa cct	gag atg	ctg agg	aaa	aaa cag	atc act	gta ctg	gat ctc	5160
Glu Pro	Glu Met	Leu Arg	Lys	Lys Gln	Ile Thr	Val Leu	Asp Leu	
1675			1680			1685		
cat ccc	ggc gcc	ggt aaa	aca	agg agg	att ctg	cca cag	atc atc	5205
His Pro	Gly Ala	Gly Lys	Thr	Arg Arg	Ile Leu	Pro Gln	Ile Ile	
1690			1695			1700		
aaa gag	gcc ata	aac aga	aga	ctg aga	aca gcc	gtg cta	gca cca	5250
Lys Glu	Ala Ile	Asn Arg	Arg	Leu Arg	Thr Ala	Val Leu	Ala Pro	
1705			1710			1715		
acc agg	gtt gtg	gct gct	gag	atg gct	gaa gca	ctg aga	gga ctg	5295
Thr Arg	Val Val	Ala Ala	Glu	Met Ala	Glu Ala	Leu Arg	Gly Leu	
1720			1725			1730		
ccc atc	cgg tac	cag aca	tcc	gca gtg	ccc aga	gaa cat	aat gga	5340
Pro Ile	Arg Tyr	Gln Thr	Ser	Ala Val	Pro Arg	Glu His	Asn Gly	
1735			1740			1745		
aat gag	att gtt	gat gtc	atg	tgt cat	gct acc	ctc acc	cac agg	5385
Asn Glu	Ile Val	Asp Val	Met	Cys His	Ala Thr	Leu Thr	His Arg	
1750			1755			1760		
ctg atg	tct cct	cac agg	gtg	ccg aac	tac aac	ctg ttc	gtg atg	5430
Leu Met	Ser Pro	His Arg	Val	Pro Asn	Tyr Asn	Leu Phe	Val Met	
1765			1770			1775		
gat gag	gct cat	ttc acc	gac	cca gct	agc att	gca gca	aga ggt	5475
Asp Glu	Ala His	Phe Thr	Asp	Pro Ala	Ser Ile	Ala Ala	Arg Gly	
1780			1785			1790		
tac att	tcc aca	aag gtc	gag	cta ggg	gag gcg	gcg gca	ata ttc	5520
Tyr Ile	Ser Thr	Lys Val	Glu	Leu Gly	Glu Ala	Ala Ala	Ile Phe	
1795			1800			1805		
atg aca	gcc acc	cca cca	ggc	act tca	gat cca	ttc cca	gag tcc	5565
Met Thr	Ala Thr	Pro Pro	Gly	Thr Ser	Asp Pro	Phe Pro	Glu Ser	
1810			1815			1820		
aat tca	cca att	tcc gac	tta	cag act	gag atc	ccg gat	cga gct	5610
Asn Ser	Pro Ile	Ser Asp	Leu	Gln Thr	Glu Ile	Pro Asp	Arg Ala	
1825			1830			1835		
tgg aac	tct gga	tac gaa	tgg	atc aca	gaa tac	acc ggg	aag acg	5655
Trp Asn	Ser Gly	Tyr Glu	Trp	Ile Thr	Glu Tyr	Thr Gly	Lys Thr	
1840			1845			1850		
gtt tgg	ttt gtg	cct agt	gtc	aag atg	ggg aat	gag att	gcc ctt	5700
Val Trp	Phe Val	Pro Ser	Val	Lys Met	Gly Asn	Glu Ile	Ala Leu	
1855			1860			1865		
tgc cta	caa cgt	gct gga	aag	aaa gta	gtc caa	ttg aac	aga aag	5745
Cys Leu	Gln Arg	Ala Gly	Lys	Lys Val	Val Gln	Leu Asn	Arg Lys	
1870			1875			1880		
tcg tac	gag acg	gag tac	cca	aaa tgt	aag aac	gat gat	tgg gac	5790
Ser Tyr	Glu Thr	Glu Tyr	Pro	Lys Cys	Lys Asn	Asp Asp	Trp Asp	
1885			1890			1895		
ttt gtt	atc aca	aca gac	ata	tct gaa	atg ggg	gct aac	ttc aag	5835
Phe Val	Ile Thr	Thr Asp	Ile	Ser Glu	Met Gly	Ala Asn	Phe Lys	
1900			1905			1910		
gcg agc	agg gtg	att gac	agc	cgg aag	agt gtg	aaa cca	acc atc	5880
Ala Ser	Arg Val	Ile Asp	Ser	Arg Lys	Ser Val	Lys Pro	Thr Ile	
1915			1920			1925		
ata aca	gaa gga	gaa ggg	aga	gtg atc	ctg gga	gaa cca	tct gca	5925
Ile Thr	Glu Gly	Glu Gly	Arg	Val Ile	Leu Gly	Glu Pro	Ser Ala	
1930			1935			1940		
gtg aca	gca gct	agt gcc	gcc	cag aga	cgt gga	cgt atc	ggt aga	5970
Val Thr	Ala Ala	Ser Ala	Ala	Gln Arg	Arg Gly	Arg Ile	Gly Arg	
1945			1950			1955		

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aat ccg	tcg caa gtt ggt gat	gag tac tgt tat ggg	ggg cac acg	6015
Asn Pro	Ser Gln Val Gly Asp	Glu Tyr Cys Tyr Gly	Gly His Thr	
1960	1965	1970		
aat gaa	gac gac tcg aac ttc	gcc cat tgg act gag	gca cga atc	6060
Asn Glu	Asp Asp Ser Asn Phe	Ala His Trp Thr Glu	Ala Arg Ile	
1975	1980	1985		
atg ctg	gac aac atc aac atg	cca aac gga ctg atc	gct caa ttc	6105
Met Leu	Asp Asn Ile Asn Met	Pro Asn Gly Leu Ile	Ala Gln Phe	
1990	1995	2000		
tac caa	cca gag cgt gag aag	gta tat acc atg gat	ggg gaa tac	6150
Tyr Gln	Pro Glu Arg Glu Lys	Val Tyr Thr Met Asp	Gly Glu Tyr	
2005	2010	2015		
cgg ctc	aga gga gaa gag aga	aaa aac ttt ctg gaa	ctg ttg agg	6195
Arg Leu	Arg Gly Glu Glu Arg	Lys Asn Phe Leu Glu	Leu Leu Arg	
2020	2025	2030		
act gca	gat ctg cca gtt tgg	ctg gct tac aag gtt	gca gcg gct	6240
Thr Ala	Asp Leu Pro Val Trp	Leu Ala Tyr Lys Val	Ala Ala Ala	
2035	2040	2045		
gga gtg	tca tac cac gac cgg	agg tgg tgc ttt gat	ggg cct agg	6285
Gly Val	Ser Tyr His Asp Arg	Arg Trp Cys Phe Asp	Gly Pro Arg	
2050	2055	2060		
aca aac	aca att tta gaa gac	aac aac gaa gtg gaa	gtc atc acg	6330
Thr Asn	Thr Ile Leu Glu Asp	Asn Asn Glu Val Glu	Val Ile Thr	
2065	2070	2075		
aag ctt	ggt gaa agg aag att	ctg agg ccg cgc tgg	att gac gcc	6375
Lys Leu	Gly Glu Arg Lys Ile	Leu Arg Pro Arg Trp	Ile Asp Ala	
2080	2085	2090		
agg gtg	tac tcg gat cac cag	gca cta aag gcg ttc	aag gac ttc	6420
Arg Val	Tyr Ser Asp His Gln	Ala Leu Lys Ala Phe	Lys Asp Phe	
2095	2100	2105		
gcc tcg	gga aaa cgt tct cag	ata ggg ctc att gag	gtt ctg gga	6465
Ala Ser	Gly Lys Arg Ser Gln	Ile Gly Leu Ile Glu	Val Leu Gly	
2110	2115	2120		
aag atg	cct gag cac ttc atg	ggg aag aca tgg gaa	gca ctt gac	6510
Lys Met	Pro Glu His Phe Met	Gly Lys Thr Trp Glu	Ala Leu Asp	
2125	2130	2135		
acc atg	tac gtt gtg gcc act	gca gag aaa gga gga	aga gct cac	6555
Thr Met	Tyr Val Val Ala Thr	Ala Glu Lys Gly Gly	Arg Ala His	
2140	2145	2150		
aga atg	gcc ctg gag gaa ctg	cca gat gct ctt cag	aca att gcc	6600
Arg Met	Ala Leu Glu Glu Leu	Pro Asp Ala Leu Gln	Thr Ile Ala	
2155	2160	2165		
ttg att	gcc tta ttg agt gtg	atg acc atg gga gta	ttc ttc ctc	6645
Leu Ile	Ala Leu Leu Ser Val	Met Thr Met Gly Val	Phe Phe Leu	
2170	2175	2180		
ctc atg	cag cgg aag ggc att	gga aag ata ggt ttg	gga ggc gct	6690
Leu Met	Gln Arg Lys Gly Ile	Gly Lys Ile Gly Leu	Gly Gly Ala	
2185	2190	2195		
gtc ttg	gga gtc gcg acc ttt	ttc tgt tgg atg gct	gaa gtt cca	6735
Val Leu	Gly Val Ala Thr Phe	Phe Cys Trp Met Ala	Glu Val Pro	
2200	2205	2210		
gga acg	aag atc gcc gga atg	ttg ctg ctc tcc ctt	ctc ttg atg	6780
Gly Thr	Lys Ile Ala Gly Met	Leu Leu Leu Ser Leu	Leu Leu Met	
2215	2220	2225		
att gtg	cta att cct gag cca	gag aag caa cgt tcg	cag aca gac	6825
Ile Val	Leu Ile Pro Glu Pro	Glu Lys Gln Arg Ser	Gln Thr Asp	
2230	2235	2240		
aac cag	cta gcc gtg ttc ctg	att tgt gtc atg acc	ctt gtg agc	6870
Asn Gln	Leu Ala Val Phe Leu	Ile Cys Val Met Thr	Leu Val Ser	
2245	2250	2255		

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gca gtg Ala Val 2260	gca gcc aac gag atg Ala Ala Asn Glu Met 2265	ggt tgg cta gat aag Gly Trp Leu Asp Lys 2270	acc aag agt Thr Lys Ser	6915
gac ata Asp Ile 2275	agc agt ttg ttt ggg Ser Ser Leu Phe Gly 2280	caa aga att gag gtc Gln Arg Ile Glu Val 2285	aag gag aat Lys Glu Asn	6960
ttc agc Phe Ser 2290	atg gga gag ttt ctt Met Gly Glu Phe Leu 2295	ttg gac ttg agg cct Leu Asp Leu Arg Pro 2300	gca aca gcc Ala Thr Ala	7005
tgg tca Trp Ser 2305	ctg tac gct gtg aca Leu Tyr Ala Val Thr 2310	aca gcg gtc ctc act Thr Ala Val Leu Thr 2315	cca ctg cta Pro Leu Leu	7050
aag cat Lys His 2320	ttg atc acg tca gat Leu Ile Thr Ser Asp 2325	tac atc aac acc tca Tyr Ile Asn Thr Ser 2330	ttg acc tca Leu Thr Ser	7095
ata aac Ile Asn 2335	ggt cag gca agt gca Val Gln Ala Ser Ala 2340	cta ttc aca ctc gcg Leu Phe Thr Leu Ala 2345	cga ggc ttc Arg Gly Phe	7140
ccc ttc Pro Phe 2350	gtc gat gtt gga gtg Val Asp Val Gly Val 2355	tcg gct ctc ctg cta Ser Ala Leu Leu Leu 2360	gca gcc gga Ala Ala Gly	7185
tgc tgg Cys Trp 2365	gga caa gtc acc ctc Gly Gln Val Thr Leu 2370	acc gtt acg gta aca Thr Val Thr Val Thr 2375	gcg gca aca Ala Ala Thr	7230
ctc ctt Leu Leu 2380	ttt tgc cac tat gcc Phe Cys His Tyr Ala 2385	tac atg gtt ccc ggt Tyr Met Val Pro Gly 2390	tgg caa gct Trp Gln Ala	7275
gag gca Glu Ala 2395	atg cgc tca gcc cag Met Arg Ser Ala Gln 2400	cgg cgg aca gcg gcc Arg Arg Thr Ala Ala 2405	gga atc atg Gly Ile Met	7320
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tac cgc Tyr Arg 2545	aaa gag gcc atc atc Lys Glu Ala Ile Ile 2550	gaa gtc gat cgc tca Glu Val Asp Arg Ser 2555	gcg gca aaa Ala Ala Lys	7770

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gaa ccg Glu Pro 2590	gtc gga aaa gtg att Val Gly Lys Val Ile 2595	gac ctt gga tgt gga Asp Leu Gly Cys Gly 2600	aga ggc ggt Arg Gly Gly 2605	7905
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gat gag Asp Glu 2815	aac cac cca tat aga Asn His Pro Tyr Arg 2820	acc tgg aac tat cac Thr Trp Asn Tyr His 2825	ggc agt tat Gly Ser Tyr 2830	8580
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

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<400> SEQUENCE: 8

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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 Ser Thr Ile Thr Leu Leu Cys
100         105         110
Leu Ile Pro Thr Val Met Ala Phe His Leu Ser Thr Arg Asp Gly Glu
115         120         125
Pro Leu Met Ile Val Ala Lys His Glu Arg Gly Arg Pro Leu Leu Phe
130         135         140
Lys Thr Thr Glu Gly Ile Asn Lys Cys Thr Leu Ile Ala Met Asp Leu
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Gly Glu Met Cys Glu Asp Thr Val Thr Tyr Lys Cys Pro Leu Leu Val
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Asn Thr Glu Pro Glu Asp Ile Asp Cys Trp Cys Asn Leu Thr Ser Thr
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Trp Val Met Tyr Gly Thr Cys Thr Gln Ser Gly Glu Arg Arg Arg Glu
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Lys Arg Ser Val Ala Leu Thr Pro His Ser Gly Met Gly Leu Glu Thr
210         215         220
Arg Ala Glu Thr Trp Met Ser Ser Glu Gly Ala Trp Lys His Ala Gln
225         230         235         240
Arg Val Glu Ser Trp Ile Leu Arg Asn Pro Gly Phe Ala Leu Leu Ala
245         250         255
Gly Phe Met Ala Tyr Met Ile Gly Gln Thr Gly Ile Gln Arg Thr Val
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Phe Phe Val Leu Met Met Leu Val Ala Pro Ser Tyr Gly Met Arg Cys
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Ile	Thr	Thr	Ala	Thr	Arg	Cys	Pro	Thr	Gln	Gly	Glu	Pro	Tyr	Leu	Lys	
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Cys	Ala	Lys	Phe	Ser	Cys	Ser	Gly	Lys	Ile	Thr	Gly	Asn	Leu	Val	Gln	
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Glu	Arg	Ala	Val	Leu	Gly	Glu	Val	Lys	Ser	Cys	Thr	Trp	Pro	Glu	Thr	
		995					1000					1005				
His	Thr	Leu	Trp	Gly	Asp	Gly	Ile	Leu	Glu	Ser	Asp	Leu	Ile	Ile		
		1010				1015					1020					
Pro	Val	Thr	Leu	Ala	Gly	Pro	Arg	Ser	Asn	His	Asn	Arg	Arg	Pro		
		1025				1030					1035					
Gly	Tyr	Lys	Thr	Gln	Asn	Gln	Gly	Pro	Trp	Asp	Glu	Gly	Arg	Val		
		1040				1045					1050					
Glu	Ile	Asp	Phe	Asp	Tyr	Cys	Pro	Gly	Thr	Thr	Val	Thr	Leu	Ser		
		1055				1060					1065					
Glu	Ser	Cys	Gly	His	Arg	Gly	Pro</									

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Arg Trp	Thr Ala Lys Ile	Ser	Met Pro Ala Ile	Leu	Ile Ala Leu
1160		1165		1170	
Leu Val	Leu Val Phe Gly	Gly	Ile Thr Tyr Thr	Asp	Val Leu Arg
1175		1180		1185	
Tyr Val	Ile Leu Val Gly	Ala	Ala Phe Ala Glu	Ser	Asn Ser Gly
1190		1195		1200	
Gly Asp	Val Val His Leu	Ala	Leu Met Ala Thr	Phe	Lys Ile Gln
1205		1210		1215	
Pro Val	Phe Met Val Ala	Ser	Phe Leu Lys Ala	Arg	Trp Thr Asn
1220		1225		1230	
Gln Glu	Asn Ile Leu Leu	Met	Leu Ala Ala Val	Phe	Phe Gln Met
1235		1240		1245	
Ala Tyr	Tyr Asp Ala Arg	Gln	Ile Leu Leu Trp	Glu	Ile Pro Asp
1250		1255		1260	
Val Leu	Asn Ser Leu Ala	Val	Ala Trp Met Ile	Leu	Arg Ala Ile
1265		1270		1275	
Thr Phe	Thr Thr Thr Ser	Asn	Val Val Val Pro	Leu	Leu Ala Leu
1280		1285		1290	
Leu Thr	Pro Gly Leu Arg	Cys	Leu Asn Leu Asp	Val	Tyr Arg Ile
1295		1300		1305	
Leu Leu	Leu Met Val Gly	Ile	Gly Ser Leu Ile	Arg	Glu Lys Arg
1310		1315		1320	
Ser Ala	Ala Ala Lys Lys	Lys	Gly Ala Ser Leu	Leu	Cys Leu Ala
1325		1330		1335	
Leu Ala	Ser Thr Gly Leu	Phe	Asn Pro Met Ile	Leu	Ala Ala Gly
1340		1345		1350	
Leu Ile	Ala Cys Asp Pro	Asn	Arg Lys Arg Gly	Trp	Pro Ala Thr
1355		1360		1365	
Glu Val	Met Thr Ala Val	Gly	Leu Met Phe Ala	Ile	Val Gly Gly
1370		1375		1380	
Leu Ala	Glu Leu Asp Ile	Asp	Ser Met Ala Ile	Pro	Met Thr Ile
1385		1390		1395	
Ala Gly	Leu Met Phe Ala	Ala	Phe Val Ile Ser	Gly	Lys Ser Thr
1400		1405		1410	
Asp Met	Trp Ile Glu Arg	Thr	Ala Asp Ile Ser	Trp	Glu Ser Asp
1415		1420		1425	
Ala Glu	Ile Thr Gly Ser	Ser	Glu Arg Val Asp	Val	Arg Leu Asp
1430		1435		1440	
Asp Asp	Gly Asn Phe Gln	Leu	Met Asn Asp Pro	Gly	Ala Pro Trp
1445		1450		1455	
Lys Ile	Trp Met Leu Arg	Met	Val Cys Leu Ala	Ile	Ser Ala Tyr
1460		1465		1470	
Thr Pro	Trp Ala Ile Leu	Pro	Ser Val Val Gly	Phe	Trp Ile Thr
1475		1480		1485	
Leu Gln	Tyr Thr Lys Arg	Gly	Gly Val Leu Trp	Asp	Thr Pro Ser
1490		1495		1500	
Pro Lys	Glu Tyr Lys Lys	Gly	Asp Thr Thr Thr	Gly	Val Tyr Arg
1505		1510		1515	
Ile Met	Thr Arg Gly Leu	Leu	Gly Ser Tyr Gln	Ala	Gly Ala Gly
1520		1525		1530	
Val Met	Val Glu Gly Val	Phe	His Thr Leu Trp	His	Thr Thr Lys
1535		1540		1545	
Gly Ala	Ala Leu Met Ser	Gly	Glu Gly Arg Leu	Asp	Pro Tyr Trp
1550		1555		1560	

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Gly	Ser	Val	Lys	Glu	Asp	Arg	Leu	Cys	Tyr	Gly	Gly	Pro	Trp	Lys
1565						1570					1575			
Leu	Gln	His	Lys	Trp	Asn	Gly	Gln	Asp	Glu	Val	Gln	Met	Ile	Val
1580						1585					1590			
Val	Glu	Pro	Gly	Arg	Asn	Val	Lys	Asn	Val	Gln	Thr	Lys	Pro	Gly
1595						1600					1605			
Val	Phe	Lys	Thr	Pro	Glu	Gly	Glu	Ile	Gly	Ala	Val	Thr	Leu	Asp
1610						1615					1620			
Phe	Pro	Thr	Gly	Thr	Ser	Gly	Ser	Pro	Ile	Val	Asp	Lys	Asn	Gly
1625						1630					1635			
Asp	Val	Ile	Gly	Leu	Tyr	Gly	Asn	Gly	Val	Ile	Met	Pro	Asn	Gly
1640						1645					1650			
Ser	Tyr	Ile	Ser	Ala	Ile	Val	Gln	Gly	Glu	Arg	Met	Asp	Glu	Pro
1655						1660					1665			
Ile	Pro	Ala	Gly	Phe	Glu	Pro	Glu	Met	Leu	Arg	Lys	Lys	Gln	Ile
1670						1675					1680			
Thr	Val	Leu	Asp	Leu	His	Pro	Gly	Ala	Gly	Lys	Thr	Arg	Arg	Ile
1685						1690					1695			
Leu	Pro	Gln	Ile	Ile	Lys	Glu	Ala	Ile	Asn	Arg	Arg	Leu	Arg	Thr
1700						1705					1710			
Ala	Val	Leu	Ala	Pro	Thr	Arg	Val	Val	Ala	Ala	Glu	Met	Ala	Glu
1715						1720					1725			
Ala	Leu	Arg	Gly	Leu	Pro	Ile	Arg	Tyr	Gln	Thr	Ser	Ala	Val	Pro
1730						1735					1740			
Arg	Glu	His	Asn	Gly	Asn	Glu	Ile	Val	Asp	Val	Met	Cys	His	Ala
1745						1750					1755			
Thr	Leu	Thr	His	Arg	Leu	Met	Ser	Pro	His	Arg	Val	Pro	Asn	Tyr
1760						1765					1770			
Asn	Leu	Phe	Val	Met	Asp	Glu	Ala	His	Phe	Thr	Asp	Pro	Ala	Ser
1775						1780					1785			
Ile	Ala	Ala	Arg	Gly	Tyr	Ile	Ser	Thr	Lys	Val	Glu	Leu	Gly	Glu
1790						1795					1800			
Ala	Ala	Ala	Ile	Phe	Met	Thr	Ala	Thr	Pro	Pro	Gly	Thr	Ser	Asp
1805						1810					1815			
Pro	Phe	Pro	Glu	Ser	Asn	Ser	Pro	Ile	Ser	Asp	Leu	Gln	Thr	Glu
1820						1825					1830			
Ile	Pro	Asp	Arg	Ala	Trp	Asn	Ser	Gly	Tyr	Glu	Trp	Ile	Thr	Glu
1835						1840					1845			
Tyr	Thr	Gly	Lys	Thr	Val	Trp	Phe	Val	Pro	Ser	Val	Lys	Met	Gly
1850						1855					1860			
Asn	Glu	Ile	Ala	Leu	Cys	Leu	Gln	Arg	Ala	Gly	Lys	Lys	Val	Val
1865						1870					1875			
Gln	Leu	Asn	Arg	Lys	Ser	Tyr	Glu	Thr	Glu	Tyr	Pro	Lys	Cys	Lys
1880						1885					1890			
Asn	Asp	Asp	Trp	Asp	Phe	Val	Ile	Thr	Thr	Asp	Ile	Ser	Glu	Met
1895						1900					1905			
Gly	Ala	Asn	Phe	Lys	Ala	Ser	Arg	Val	Ile	Asp	Ser	Arg	Lys	Ser
1910						1915					1920			
Val	Lys	Pro	Thr	Ile	Ile	Thr	Glu	Gly	Glu	Gly	Arg	Val	Ile	Leu
1925						1930					1935			
Gly	Glu	Pro	Ser	Ala	Val	Thr	Ala	Ala	Ser	Ala	Ala	Gln	Arg	Arg
1940						1945					1950			
Gly	Arg	Ile	Gly	Arg	Asn	Pro	Ser	Gln	Val	Gly	Asp	Glu	Tyr	Cys
1955						1960					1965			

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Tyr Gly	Gly His Thr Asn Glu	Asp Asp Ser Asn Phe	Ala His Trp
1970	1975	1980	
Thr Glu	Ala Arg Ile Met Leu	Asp Asn Ile Asn Met	Pro Asn Gly
1985	1990	1995	
Leu Ile	Ala Gln Phe Tyr Gln	Pro Glu Arg Glu Lys	Val Tyr Thr
2000	2005	2010	
Met Asp	Gly Glu Tyr Arg Leu	Arg Gly Glu Glu Arg	Lys Asn Phe
2015	2020	2025	
Leu Glu	Leu Leu Arg Thr Ala	Asp Leu Pro Val Trp	Leu Ala Tyr
2030	2035	2040	
Lys Val	Ala Ala Ala Gly Val	Ser Tyr His Asp Arg	Arg Trp Cys
2045	2050	2055	
Phe Asp	Gly Pro Arg Thr Asn	Thr Ile Leu Glu Asp	Asn Asn Glu
2060	2065	2070	
Val Glu	Val Ile Thr Lys Leu	Gly Glu Arg Lys Ile	Leu Arg Pro
2075	2080	2085	
Arg Trp	Ile Asp Ala Arg Val	Tyr Ser Asp His Gln	Ala Leu Lys
2090	2095	2100	
Ala Phe	Lys Asp Phe Ala Ser	Gly Lys Arg Ser Gln	Ile Gly Leu
2105	2110	2115	
Ile Glu	Val Leu Gly Lys Met	Pro Glu His Phe Met	Gly Lys Thr
2120	2125	2130	
Trp Glu	Ala Leu Asp Thr Met	Tyr Val Val Ala Thr	Ala Glu Lys
2135	2140	2145	
Gly Gly	Arg Ala His Arg Met	Ala Leu Glu Glu Leu	Pro Asp Ala
2150	2155	2160	
Leu Gln	Thr Ile Ala Leu Ile	Ala Leu Leu Ser Val	Met Thr Met
2165	2170	2175	
Gly Val	Phe Phe Leu Leu Met	Gln Arg Lys Gly Ile	Gly Lys Ile
2180	2185	2190	
Gly Leu	Gly Gly Ala Val Leu	Gly Val Ala Thr Phe	Phe Cys Trp
2195	2200	2205	
Met Ala	Glu Val Pro Gly Thr	Lys Ile Ala Gly Met	Leu Leu Leu
2210	2215	2220	
Ser Leu	Leu Leu Met Ile Val	Leu Ile Pro Glu Pro	Glu Lys Gln
2225	2230	2235	
Arg Ser	Gln Thr Asp Asn Gln	Leu Ala Val Phe Leu	Ile Cys Val
2240	2245	2250	
Met Thr	Leu Val Ser Ala Val	Ala Ala Asn Glu Met	Gly Trp Leu
2255	2260	2265	
Asp Lys	Thr Lys Ser Asp Ile	Ser Ser Leu Phe Gly	Gln Arg Ile
2270	2275	2280	
Glu Val	Lys Glu Asn Phe Ser	Met Gly Glu Phe Leu	Leu Asp Leu
2285	2290	2295	
Arg Pro	Ala Thr Ala Trp Ser	Leu Tyr Ala Val Thr	Thr Ala Val
2300	2305	2310	
Leu Thr	Pro Leu Leu Lys His	Leu Ile Thr Ser Asp	Tyr Ile Asn
2315	2320	2325	
Thr Ser	Leu Thr Ser Ile Asn	Val Gln Ala Ser Ala	Leu Phe Thr
2330	2335	2340	
Leu Ala	Arg Gly Phe Pro Phe	Val Asp Val Gly Val	Ser Ala Leu
2345	2350	2355	
Leu Leu	Ala Ala Gly Cys Trp	Gly Gln Val Thr Leu	Thr Val Thr
2360	2365	2370	

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Val Thr	Ala Ala Thr Leu	Leu	Phe Cys His Tyr	Ala	Tyr Met Val
2375		2380		2385	
Pro Gly	Trp Gln Ala Glu	Ala	Met Arg Ser Ala	Gln	Arg Arg Thr
2390		2395		2400	
Ala Ala	Gly Ile Met Lys	Asn	Ala Val Val Asp	Gly	Ile Val Ala
2405		2410		2415	
Thr Asp	Val Pro Glu Leu	Glu	Arg Thr Thr Pro	Ile	Met Gln Lys
2420		2425		2430	
Lys Val	Gly Gln Ile Met	Leu	Ile Leu Val Ser	Leu	Ala Ala Val
2435		2440		2445	
Val Val	Asn Pro Ser Val	Lys	Thr Val Arg Glu	Ala	Gly Ile Leu
2450		2455		2460	
Ile Thr	Ala Ala Ala Val	Thr	Leu Trp Glu Asn	Gly	Ala Ser Ser
2465		2470		2475	
Val Trp	Asn Ala Thr Thr	Ala	Ile Gly Leu Cys	His	Ile Met Arg
2480		2485		2490	
Gly Gly	Trp Leu Ser Cys	Leu	Ser Ile Thr Trp	Thr	Leu Ile Lys
2495		2500		2505	
Asn Met	Glu Lys Pro Gly	Leu	Lys Arg Gly Gly	Ala	Lys Gly Arg
2510		2515		2520	
Thr Leu	Gly Glu Val Trp	Lys	Glu Arg Leu Asn	Gln	Met Thr Lys
2525		2530		2535	
Glu Glu	Phe Thr Arg Tyr	Arg	Lys Glu Ala Ile	Ile	Glu Val Asp
2540		2545		2550	
Arg Ser	Ala Ala Lys His	Ala	Arg Lys Glu Gly	Asn	Val Thr Gly
2555		2560		2565	
Gly His	Pro Val Ser Arg	Gly	Thr Ala Lys Leu	Arg	Trp Leu Val
2570		2575		2580	
Glu Arg	Arg Phe Leu Glu	Pro	Val Gly Lys Val	Ile	Asp Leu Gly
2585		2590		2595	
Cys Gly	Arg Gly Gly Trp	Cys	Tyr Tyr Met Ala	Thr	Gln Lys Arg
2600		2605		2610	
Val Gln	Glu Val Arg Gly	Tyr	Thr Lys Gly Gly	Pro	Gly His Glu
2615		2620		2625	
Glu Pro	Gln Leu Val Gln	Ser	Tyr Gly Trp Asn	Ile	Val Thr Met
2630		2635		2640	
Lys Ser	Gly Val Asp Val	Phe	Tyr Arg Pro Ser	Glu	Cys Cys Asp
2645		2650		2655	
Thr Leu	Leu Cys Asp Ile	Gly	Glu Ser Ser Ser	Ser	Ala Glu Val
2660		2665		2670	
Glu Glu	His Arg Thr Ile	Arg	Val Leu Glu Met	Val	Glu Asp Trp
2675		2680		2685	
Leu His	Arg Gly Pro Arg	Glu	Phe Cys Val Lys	Val	Leu Cys Pro
2690		2695		2700	
Tyr Met	Pro Lys Val Ile	Glu	Lys Met Glu Leu	Leu	Gln Arg Arg
2705		2710		2715	
Tyr Gly	Gly Gly Leu Val	Arg	Asn Pro Leu Ser	Arg	Asn Ser Thr
2720		2725		2730	
His Glu	Met Tyr Trp Val	Ser	Arg Ala Ser Gly	Asn	Val Val His
2735		2740		2745	
Ser Val	Asn Met Thr Ser	Gln	Val Leu Leu Gly	Arg	Met Glu Lys
2750		2755		2760	
Arg Thr	Trp Lys Gly Pro	Gln	Tyr Glu Glu Asp	Val	Asn Leu Gly
2765		2770		2775	

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Ser Gly 2780	Thr Arg Ala Val 2785	Gly Lys Pro Leu Leu 2790	Asn Ser Asp Thr 2790
Ser Lys 2795	Ile Lys Asn Arg 2800	Glu Arg Leu Arg 2805	Arg Glu Tyr Ser 2805
Ser Thr 2810	Trp His His Asp 2815	Glu Asn His Pro Tyr 2820	Arg Thr Trp Asn 2820
Tyr His 2825	Gly Ser Tyr Asp 2830	Val Lys Pro Thr Gly 2835	Ser Ala Ser Ser 2835
Leu Val 2840	Asn Gly Val Val 2845	Arg Leu Leu Ser Lys 2850	Pro Trp Asp Thr 2850
Ile Thr 2855	Asn Val Thr Thr 2860	Met Ala Met Thr Asp 2865	Thr Thr Pro Phe 2865
Gly Gln 2870	Gln Arg Val Phe 2875	Lys Glu Lys Val Asp 2880	Thr Lys Ala Pro 2880
Glu Pro 2885	Pro Glu Gly Val 2890	Lys Tyr Val Leu Asn 2895	Glu Thr Thr Asn 2895
Trp Leu 2900	Trp Ala Phe Leu 2905	Ala Arg Glu Lys Arg 2910	Pro Arg Met Cys 2910
Ser Arg 2915	Glu Glu Phe Ile 2920	Arg Lys Val Asn Ser 2925	Asn Ala Ala Leu 2925
Gly Ala 2930	Met Phe Glu Glu 2935	Gln Asn Gln Trp Arg 2940	Ser Ala Arg Glu 2940
Ala Val 2945	Glu Asp Pro Lys 2950	Phe Trp Glu Met Val 2955	Asp Glu Glu Arg 2955
Glu Ala 2960	His Leu Arg Gly 2965	Glu Cys His Thr Cys 2970	Ile Tyr Asn Met 2970
Met Gly 2975	Lys Arg Glu Lys 2980	Lys Pro Gly Glu Phe 2985	Gly Lys Ala Lys 2985
Gly Ser 2990	Arg Ala Ile Trp 2995	Phe Met Trp Leu Gly 3000	Ala Arg Phe Leu 3000
Glu Phe 3005	Glu Ala Leu Gly 3010	Phe Leu Asn Glu Asp 3015	His Trp Leu Gly 3015
Arg Lys 3020	Asn Ser Gly Gly 3025	Gly Val Glu Gly Leu 3030	Gly Leu Gln Lys 3030
Leu Gly 3035	Tyr Ile Leu Arg 3040	Glu Val Gly Thr Arg 3045	Pro Gly Gly Lys 3045
Ile Tyr 3050	Ala Asp Asp Thr 3055	Ala Gly Trp Asp Thr 3060	Arg Ile Thr Arg 3060
Ala Asp 3065	Leu Glu Asn Glu 3070	Ala Lys Val Leu Glu 3075	Leu Leu Asp Gly 3075
Glu His 3080	Arg Arg Leu Ala 3085	Arg Ala Ile Ile Glu 3090	Leu Thr Tyr Arg 3090
His Lys 3095	Val Val Lys Val 3100	Met Arg Pro Ala Ala 3105	Asp Gly Arg Thr 3105
Val Met 3110	Asp Val Ile Ser 3115	Arg Glu Asp Gln Arg 3120	Gly Ser Gly Gln 3120
Val Val 3125	Thr Tyr Ala Leu 3130	Asn Thr Phe Thr Asn 3135	Leu Ala Val Gln 3135
Leu Val 3140	Arg Met Met Glu 3145	Gly Glu Gly Val Ile 3150	Gly Pro Asp Asp 3150
Val Glu 3155	Lys Leu Thr Lys 3160	Gly Lys Gly Pro Lys 3165	Val Arg Thr Trp 3165
Leu Phe 3170	Glu Asn Gly Glu 3175	Glu Arg Leu Ser Arg 3180	Met Ala Val Ser 3180

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Gly	Asp	Asp	Cys	Val	Val	Lys	Pro	Leu	Asp	Asp	Arg	Phe	Ala	Thr
3185						3190					3195			
Ser	Leu	His	Phe	Leu	Asn	Ala	Met	Ser	Lys	Val	Arg	Lys	Asp	Ile
3200						3205					3210			
Gln	Glu	Trp	Lys	Pro	Ser	Thr	Gly	Trp	Tyr	Asp	Trp	Gln	Gln	Val
3215						3220					3225			
Pro	Phe	Cys	Ser	Asn	His	Phe	Thr	Glu	Leu	Ile	Met	Lys	Asp	Gly
3230						3235					3240			
Arg	Thr	Leu	Val	Val	Pro	Cys	Arg	Gly	Gln	Asp	Glu	Leu	Val	Gly
3245						3250					3255			
Arg	Ala	Arg	Ile	Ser	Pro	Gly	Ala	Gly	Trp	Asn	Val	Arg	Asp	Thr
3260						3265					3270			
Ala	Cys	Leu	Ala	Lys	Ser	Tyr	Ala	Gln	Met	Trp	Leu	Leu	Leu	Tyr
3275						3280					3285			
Phe	His	Arg	Arg	Asp	Leu	Arg	Leu	Met	Ala	Asn	Ala	Ile	Cys	Ser
3290						3295					3300			
Ala	Val	Pro	Val	Asn	Trp	Val	Pro	Thr	Gly	Arg	Thr	Thr	Trp	Ser
3305						3310					3315			
Ile	His	Ala	Gly	Gly	Glu	Trp	Met	Thr	Thr	Glu	Asp	Met	Leu	Glu
3320						3325					3330			
Val	Trp	Asn	Arg	Val	Trp	Ile	Glu	Glu	Asn	Glu	Trp	Met	Glu	Asp
3335						3340					3345			
Lys	Thr	Pro	Val	Glu	Lys	Trp	Ser	Asp	Val	Pro	Tyr	Ser	Gly	Lys
3350						3355					3360			
Arg	Glu	Asp	Ile	Trp	Cys	Gly	Ser	Leu	Ile	Gly	Thr	Arg	Ala	Arg
3365						3370					3375			
Ala	Thr	Trp	Ala	Glu	Asn	Ile	Gln	Val	Ala	Ile	Asn	Gln	Val	Arg
3380						3385					3390			
Ala	Ile	Ile	Gly	Asp	Glu	Lys	Tyr	Val	Asp	Tyr	Met	Ser	Ser	Leu
3395						3400					3405			
Lys	Arg	Tyr	Glu	Asp	Thr	Thr	Leu	Val	Glu	Asp	Thr	Val	Leu	
3410						3415					3420			

<210> SEQ ID NO 9
 <211> LENGTH: 75
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Dengue 2 virus C protien/prM protein junction
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1)..(75)

<400> SEQUENCE: 9

aga	cgc	aga	tct	gca	ggc	atg	atc	att	atg	ctg	att	cca	aca	gtg	atg	48
Arg	Arg	Arg	Ser	Ala	Gly	Met	Ile	Ile	Met	Leu	Ile	Pro	Thr	Val	Met	
1			5				10					15				
gcg	ttc	cat	tta	acc	aca	cgt	aac	gga								75
Ala	Phe	His	Leu	Thr	Thr	Arg	Asn	Gly								
			20				25									

<210> SEQ ID NO 10
 <211> LENGTH: 25
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Construct

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<400> SEQUENCE: 10

Arg Arg Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val Met
 1 5 10 15

Ala Phe His Leu Thr Thr Arg Asn Gly
 20 25

<210> SEQ ID NO 11

<211> LENGTH: 75

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: West Nile virus/Dengue 2 virus chimera C protein/prM protein junction

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(75)

<400> SEQUENCE: 11

aag aaa aga tcc gcg ggc atg atc att atg ctg att cca aca gtg atg 48
 Lys Lys Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val Met
 1 5 10 15

gcg ttc cat tta acc aca cgt aac gga 75
 Ala Phe His Leu Thr Thr Arg Asn Gly
 20 25

<210> SEQ ID NO 12

<211> LENGTH: 25

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 12

Lys Lys Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val Met
 1 5 10 15

Ala Phe His Leu Thr Thr Arg Asn Gly
 20 25

<210> SEQ ID NO 13

<211> LENGTH: 87

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: West Nile virus C protein/prM protein junction

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(87)

<400> SEQUENCE: 13

aag aaa aga gga gga aag acc gga att gca gtc atg att ggc ctg atc 48
 Lys Lys Arg Gly Gly Lys Thr Gly Ile Ala Val Met Ile Gly Leu Ile
 1 5 10 15

gcc agc gta gga gca gtt acc ctc tct aac ttc caa ggg 87
 Ala Ser Val Gly Ala Val Thr Leu Ser Asn Phe Gln Gly
 20 25

<210> SEQ ID NO 14

<211> LENGTH: 29

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

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<400> SEQUENCE: 14

Lys Lys Arg Gly Gly Lys Thr Gly Ile Ala Val Met Ile Gly Leu Ile
 1 5 10 15

Ala Ser Val Gly Ala Val Thr Leu Ser Asn Phe Gln Gly
 20 25

<210> SEQ ID NO 15

<211> LENGTH: 75

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: West Nile virus/Dengue 1 virus chimera C
 protein/prM protein junction

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(75)

<400> SEQUENCE: 15

aag aaa aga tcc gtg acc atg ctc ctt atg ctg ctg ccc aca gcc ctg 48
 Lys Lys Arg Ser Val Thr Met Leu Leu Met Leu Leu Pro Thr Ala Leu
 1 5 10 15

gcg ttc cat ctg acg aca cga ggg gga 75
 Ala Phe His Leu Thr Thr Arg Gly Gly
 20 25

<210> SEQ ID NO 16

<211> LENGTH: 25

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 16

Lys Lys Arg Ser Val Thr Met Leu Leu Met Leu Leu Pro Thr Ala Leu
 1 5 10 15

Ala Phe His Leu Thr Thr Arg Gly Gly
 20 25

<210> SEQ ID NO 17

<211> LENGTH: 75

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: West Nile virus/Dengue 3 virus chimera C
 protein/prM protein chimera

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(75)

<400> SEQUENCE: 17

aag aaa aga aca tcg ctc tgt ctc atg atg atg tta cca gca aca ctt 48
 Lys Lys Arg Thr Ser Leu Cys Leu Met Met Met Leu Pro Ala Thr Leu
 1 5 10 15

gct ttc cac tta act tca cga gat gga 75
 Ala Phe His Leu Thr Ser Arg Asp Gly
 20 25

<210> SEQ ID NO 18

<211> LENGTH: 25

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

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<400> SEQUENCE: 18

Lys Lys Arg Thr Ser Leu Cys Leu Met Met Met Leu Pro Ala Thr Leu
 1 5 10 15

Ala Phe His Leu Thr Ser Arg Asp Gly
 20 25

<210> SEQ ID NO 19

<211> LENGTH: 75

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: West Nile virus/Dengue 4 virus C protein/prM
protein junction

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(75)

<400> SEQUENCE: 19

aag aaa aga tca acg ata aca ttg ctg tgc ttg att ccc acc gta atg 48
 Lys Lys Arg Ser Thr Ile Thr Leu Leu Cys Leu Ile Pro Thr Val Met
 1 5 10 15

gcg ttt cac ttg tca aca aga gat ggc 75
 Ala Phe His Leu Ser Thr Arg Asp Gly
 20 25

<210> SEQ ID NO 20

<211> LENGTH: 25

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 20

Lys Lys Arg Ser Thr Ile Thr Leu Leu Cys Leu Ile Pro Thr Val Met
 1 5 10 15

Ala Phe His Leu Ser Thr Arg Asp Gly
 20 25

40

We claim:

1. A nucleic acid chimera comprising:
 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 from a West Nile virus genome; and
 a second nucleic acid molecule operably linked to the first nucleic acid molecule, encoding at least a portion of a prM protein and E protein from a Dengue virus genome.
2. The chimera of claim 1, wherein the West Nile virus genome is a NY99 West Nile virus strain genome.
3. The chimera of claim 1, wherein the Dengue virus genome is a Dengue-1, Dengue-2, Dengue-3, or Dengue-4 genome.
4. The chimera of claim 1, wherein the Dengue virus genome comprises a 16681 Dengue-2 virus strain genome.
5. The chimera of claim 1, wherein the second nucleic acid molecule encodes at least one amino acid substitution in the E protein, wherein the substitution increases virus titer, replication rate, plaque size, or stability in cell culture.
6. The chimera of claim 5, wherein the at least one amino acid substitution in the E protein comprises a substitution at amino acid position 64, 122, 186, 203, or a combination of two or more thereof.
7. The chimera of claim 6, wherein the at least one amino acid substitution in the E protein is one or more of K122I, S186F, and N203D.
8. The chimera of claim 1, wherein the second nucleic acid molecule encodes at least one amino acid substitution in the prM protein, wherein the substitution increases virus titer, replication rate, plaque size, or stability in cell culture.
9. The chimera of claim 1, wherein the first nucleic acid molecule encodes at least one amino acid substitution in one or more of the non-structural proteins or the C protein, wherein the substitution increases virus titer, replication rate, plaque size, or stability in cell culture, or decreases infectivity in mosquitoes.
10. The chimera of claim 9, wherein the amino acid substitution is a substitution selected from the group consisting of position 49 of non-structural protein 2A (NS2A), position 94 of NS2A, position 241 of non-structural protein 4B (NS4B), and a combination of two or more thereof.
11. The chimera of claim 10, wherein the amino acid substitution is one or more of NS2A I49T, NS2A F94L, and NS4B T241I.
12. The chimera of claim 1, wherein the first nucleic acid molecule comprises at least one nucleic acid substitution in the 5' non-coding region or the 3' non-coding region of the West Nile virus genome, wherein the substitution increases virus titer, replication rate, plaque size, or stability in cell culture, or decreases infectivity in mosquitoes.
13. The chimera of claim 1, wherein the second nucleic acid molecule encodes at least one amino acid substitution in

201

the E protein, wherein the substituted E-protein exhibits measurably reduced antibody cross-reactivity.

14. The chimera of claim 13, wherein the at least one amino acid substitution in the E protein comprises a substitution at amino acid position 101, 106, 107, 108, 135, or a combination of two or more thereof.

15. The chimera of claim 1, having a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, and nucleic acid sequences at least 95% identical to at least one of SEQ ID NOs: 1, 3, 5, or 7.

16. The chimera of claim 1, having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, and amino acid sequences at least 95% identical to at least one of SEQ ID NOs: 2, 4, 6, or 8.

17. A method of detecting a Dengue virus antibody in a sample from a subject, comprising:

contacting the sample with a virus encoded by the chimera of claim 1 to form a virus-sample mixture;

inoculating a susceptible monolayer cell culture with the virus-sample mixture;

incubating the cell culture under conditions sufficient to allow virus replication;

counting plaques, counting immunostained foci, or measuring viral antigen level in the culture; and

comparing the number of plaques, the number of foci, or the viral antigen level to a control culture, wherein a decrease in the number of plaques, number of foci, or viral antigen level as compared to the control culture indicates the Dengue virus antibody is present in the sample.

202

18. A method of evaluating efficacy of a candidate Dengue virus vaccine, comprising:

immunizing a set of subjects with the candidate Dengue virus vaccine;

waiting sufficient time for an immune response to develop; challenging the subjects by inoculating the subjects with a virus encoded by the chimera of claim 1;

waiting sufficient time for viremia, morbidity and/or mortality to develop; and

comparing viremia, morbidity and/or mortality of the subjects with a set of non-immunized control subjects which has not been immunized with the candidate Dengue virus vaccine, wherein a decrease in viremia, morbidity and/or mortality as compared with the control subjects indicates efficacy of the candidate Dengue virus vaccine.

19. A method of producing virus particles expressing Dengue virus prM, M, and E proteins, comprising:

culturing a virus encoded by the chimera of claim 1 in a cell, wherein virus particles comprising one or more Dengue prM, M, or E proteins are produced;

collecting a supernatant from the cell culture containing the chimera; and

purifying the virus particles from the supernatant.

20. A chimeric flavivirus or virus particle comprising the nucleic acid chimera of claim 1.

21. A mouse inoculated with the nucleic acid chimera of claim 1.

22. A mouse inoculated with a chimeric flavivirus or virus particle comprising the nucleic acid chimera of claim 1.

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