(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 October 2016 (20.10.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/168417 A2

(51) International Patent Classification:
C12Q 1/70 (2006.01)

(21) International Application Number:
PCT/US2016/027466

(22) International Filing Date:
14 April 2016 (14.04.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/147,354 14 April 2015 (14.04.2015) US

(71) Applicant: **VANDERBILT UNIVERSITY** [US/US]; 305 Kirkland Hall, 2201 West End Avenue, Nashville, TN 37240 (US).

(72) Inventors: **CROWE, James, E.**; 2101 20th Ave. South, Nashville, TN 37212 (US). **SMITH, Scott, A.**; 1140 Leatherwood Road, White Bluff, TN 37187 (US). **DERMODY, Terence**; 203 Derby Glen Lane, Brentwood, TN 37027 (US). **SILVA, Laurie**; 512 Westcrest Dr., Nashville, TN 37211 (US).

(74) Agent: **HIGHLANDER, Steven, L.**; Parker Highlander PLLC, 1120 S. Capital Of Texas Highway, Building One, Suite 200, Austin, TX 78746 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2016/168417 A2

(54) Title: ANTIBODY-MEDIATED NEUTRALIZATION OF CHIKUNGUNYA VIRUS

(57) Abstract: The present disclosure is directed to antibodies binding to and neutralizing Chikungunya virus (CHIKV) and methods for use thereof.

DESCRIPTION

ANTIBODY-MEDIATED NEUTRALIZATION OF CHIKUNGUNYA VIRUS

This application claims benefit of priority to U.S. Provisional Application Serial No. 62/147,354, filed April 14, 2015, the entire contents of which are hereby incorporated by reference.

BACKGROUND

This invention was made with government support under grant numbers K08 AI103038, F32 AI096833, and U54 AI057157 awarded by the National Institutes of Health. The government has certain rights in the invention.

1. Field of the Disclosure

The present disclosure relates generally to the fields of medicine, infectious disease, and immunology. More particular, the disclosure relates to antibodies that neutralize Chikungunya virus.

2. Background

Chikungunya virus (CHIKV) is an enveloped, positive-sense RNA virus in the Alphavirus genus of the *Togaviridae* family and is transmitted by *Aedes* mosquitoes. The mature CHIKV virion contains two glycoproteins, E1 and E2, which are generated from a precursor polyprotein, p62-E1, by proteolytic cleavage. E2 functions in viral attachment, whereas E1 mediates membrane fusion to allow viral entry (Kielian *et al.*, 2010). In humans, CHIKV infection causes fever and joint pain, which may be severe and last in some cases for years (Schilte *et al.*, 2013; Sissoko *et al.*, 2009; Staples *et al.*, 2009). CHIKV has caused outbreaks in most regions of sub-Saharan Africa and also in parts of Asia, Europe, and the Indian and Pacific Oceans. In December 2013, the first transmission of CHIKV in the Western Hemisphere occurred, with autochthonous cases identified in St. Martin (CDC 2013). The virus spread rapidly to virtually all islands in the Caribbean as well as Central, South, and North America. In less than one year, over a million suspected CHIKV cases in the Western Hemisphere were reported, and endemic transmission in more than 40 countries, including the United States was documented (CDC, 2014). At present, there is no licensed vaccine or antiviral therapy to prevent or treat CHIKV infection.

Although mechanisms of protective immunity to CHIKV infection in humans are not fully understood, the humoral response controls infection and limits tissue injury (Chu *et al.*, 2013; Hallengard *et al.*, 2014; Hawman *et al.*, 2013; Kam *et al.*, 2012b; Lum *et al.*, 2013; Pal *et al.*, 2013). Immune human γ-globulin neutralizes infectivity in cultured cells and prevents morbidity in mice when administered up to 24 hours after viral inoculation (Couderc *et al.*, 2009). Several murine monoclonal antibodies (mAbs) that neutralize CHIKV infection have been described (Brehin *et al.*, 2008; Goh *et al.*, 2013; Masrinoul *et al.*, 2014; Pal *et al.*, 2013; Pal *et al.*, 2014), including some with efficacy when used in combination to treat mice or nonhuman primates following CHIKV challenge (Pal *et al.*, 2013; Pal *et al.*, 2014). In comparison, a limited number of human CHIKV mAbs have been reported, the vast majority of which exhibit modest neutralizing activity (Fong *et al.*, 2014; Fric *et al.*, 2013; Lee *et al.*, 2011; Selvarajah *et al.*, 2013; Warter *et al.*, 2011).

SUMMARY

Thus, in accordance with the present disclosure, there is provided a method of detecting a Chikungunya virus infection in a subject comprising (a) contacting a sample from said subject with an antibody or antibody fragment having clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively; and (b) detecting Chikungunya virus glycoprotein E2 in said sample by binding of said antibody or antibody fragment to E2 in said sample. The sample may be a body fluid, such as blood, sputum, tears, saliva, mucous or serum, urine or feces. Detection may comprise ELISA, RIA or Western blot. The method may further comprise performing steps (a) and (b) a second time and determining a change in the E2 levels as compared to the first assay. The antibody may be encoding by clone-paired variable sequences as set forth in Table 1, or encoded by light and heavy chain variable sequences having 70%, 80%, 90% or 95% identity to clone-paired variable sequences as set forth in Table 1, or having light and heavy chain variable sequences characterized by clone-paired sequences as set forth in Table 2, or having 70%, 80%, 90% or 95% identity to clone-paired sequences from Table 2. The antibody fragment may be a recombinant ScFv (single chain fragment variable) antibody, Fab fragment, $F(ab')_2$ fragment, or Fv fragment. The antibody may be an IgG, and/or a chimeric antibody.

In another embodiment, there is provided a method of treating a subject infected with Chikungunya Virus, or reducing the likelihood of infection of a subject at risk of contracting Chikungunya virus, comprising delivering to said subject an antibody or antibody fragment having clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively. The antibody may be encoding by clone-paired variable sequences as set forth in Table 1, or encoded by light and heavy chain variable sequences having 70%, 80%, 90% or 95% identity to clone-paired variable sequences as set forth in Table 1, or having light and heavy chain variable sequences characterized by clone-paired sequences as set forth in Table 2, or having 70%, 80%, 90% or 95% identity to clone-paired sequences from Table 2. The antibody fragment may be a recombinant ScFv (single chain fragment variable) antibody, Fab fragment, $F(ab')_2$ fragment, or Fv fragment. The antibody may be an IgG, and/or a chimeric antibody. The antibody or antibody fragment may be administered prior to infection, or after infection. Delivering may comprise antibody or antibody fragment administration, or genetic delivery with an RNA or DNA sequence or vector encoding the antibody or antibody fragment.

In still yet another embodiment, there is provided a monoclonal antibody, wherein the antibody is characterized by clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively. The antibody may be encoding by clone-paired variable sequences as set forth in Table 1, or encoded by light and heavy chain variable sequences having 70%, 80%, 90% or 95% identity to clone-paired variable sequences as set forth in Table 1, or having light and heavy chain variable sequences characterized by clone-paired sequences as set forth in Table 2, or having 70%, 80%, 90% or 95% identity to clone-paired sequences from Table 2. The antibody fragment may be a recombinant ScFv (single chain fragment variable) antibody, Fab fragment, $F(ab')_2$ fragment, or Fv fragment. The antibody may be a chimeric antibody, or a bispecific antibody that targets a Chikungunya virus antigen other than glycoprotein. The antibody may be an IgG. The antibody or antibody fragment further comprises a cell penetrating peptide and/or is an intrabody.

Also provided is a hybridoma or engineered cell encoding an antibody or antibody fragment wherein the antibody or antibody fragment is characterized by clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively. The antibody or antibody fragment may be encoding by clone-paired variable sequences as set forth in Table 1, or encoded by light and heavy chain variable sequences having 70%, 80%, 90% or 95% identity to clone-paired variable sequences as set forth in Table 1, or having light and heavy chain variable sequences characterized by clone-paired sequences as set forth in Table 2, or having 70%, 80%, 90% or 95% identity to clone-paired sequences from Table 2. The antibody fragment may be a recombinant ScFv (single chain fragment variable) antibody, Fab fragment, $F(ab')_2$ fragment, or Fv fragment. The antibody may be a chimeric antibody, and/or an IgG. The antibody or antibody fragment further may comprise a cell penetrating peptide and/or is an intrabody.

In one embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2, comprises heavy and light chain variable sequence pairs selected from the group consisting of SEQ ID NOs: 53/54, 55/56. 57/58. 59/60, 61/62, 63/64, 65/66, 67/68, 70/71, 72/73, 74/75, 76/77, 81/82, 83/84, 85/86. 87/88, 89/90, 91/92, 93/94, 95/96, and 97/98.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 103, 104 and 105, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 187, 188 and 189, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 106, 107 and 108, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 190, 191 and 192, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 109, 110 and 111, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 193, 194 and 195, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 112, 113 and 114, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 196, 197 and 198, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 115, 116 and 117, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 199, 200 and 201, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 118, 119 and 120, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 202, 203 and 204, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 121, 122 and 123, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 205, 206 and 207, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 124, 125 and 126, respectively

and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 208, 209 and 210, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 130, 131 and 132, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 211, 212 and 213, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 133, 134 and 135, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 214, 215 and 216, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 136, 137 and 138, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 217, 218 and 219, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 139, 140 and 141, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 220, 221 and 222, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 151, 152 and 153, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 223, 224 and 225, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 154, 155 and 156, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 226, 227 and 228, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1,

CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 157, 158 and 159, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 229, 230 and 231, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 160, 161 and 162, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 232, 233 and 234, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 163, 164 and 165, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 235, 236 and 237, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 166, 167 and 168, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 238, 239 and 240, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 169, 170 and 171, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 241, 242 and 243, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 172, 173 and 174, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 244, 245, and 246, respectively.

In one embodiment, the isolated monoclonal antibody or antigen binding fragment thereof that specifically binds to Chikungunya virus glycoprotein E2 comprises the CDRH1, CDRH2 and CDRH3 amino acid sequences of SEQ ID NOs: 175, 176 and 177, respectively and CDRL1, CDRL2 and CDRL3 amino acid sequences of SEQ ID NOs: 247, 248 and 249, respectively.

The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one." The word "about" means plus or minus 5% of the stated number.

It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein. Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure. The disclosure may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIGS. 1A-C. Structural analysis of E2 residues important for mAb binding. (FIG. 1A) Sequence alignment of E2 from the CHIKV strains used in this study. Strain name is indicated on the left (S27, SEQ ID NO: 1, Accession number AF369024.2; SL15649, Accession number GU189061; LR2006_OPY1, Accession number DQ443544.2; 99659, Accession number KJ451624; RSU1, Accession number HM045797.1; NI 64 IbH35, Accession number HM045786.1). The numbers above the sequence correspond to the amino acid position in the mature E2 protein. Amino acids identical to strain S27 are indicated by a dash. Domains of E2 determined from the crystal structure of the CHIKV E2/E1 heterodimer (Voss *et al.*, 2010) are depicted in the diagram above the sequence alignment and are color-coded (cyan: domain A, purple: β-ribbon connector, green: domain B, pink: domain C, taupe shades: regions not present in the crystal structure). The position of residues at which alanine substitution disrupts mAb binding, as determined by alanine-scanning mutagenesis, are designated by color-coded dots above the alignment for each specific antibody. Residues that influence the binding of multiple antibodies are indicated by squares shaded in gray, with the darker the shade of gray, the greater number of antibodies influenced by the alanine substitution at that

residue. (FIG. 1B) Location of residues required for mAb binding mapped onto the crystal structure of the mature envelope glycoprotein complex (PDB ID 3N41). A side view of a ribbon trace of a single heterodimer of E1/E2 is shown with E1 colored in light cyan and the domains of E2 colored as in panel A. The side chains of the amino acids required for antibody binding are shown as space-filling forms and color-coded for each of the 20 individual antibodies according to the legend in panel A. Residues that influence the binding of multiple antibodies are depicted in shades of gray with the darker the shade, the greater the number of antibodies influenced by alanine substitution at that residue (legend shown on the left). (FIG. 1C) A top view of the E1/E2 heterodimer, rotated 90° from the structure in FIG. 1B.

FIGS. 2A-B. Mechanism of neutralization by human anti-CHIKV mAbs. (FIG. 2A) Pre- and post-attachment neutralization assays. SL15649 VRPs were (i) incubated with the mAbs shown (including CHK-152, a positive control mAb) at 4°C for 1 hour prior to addition to pre-chilled Vero cells, followed by removal of unbound virus by three washes (pre-attachment; filled circle) or (ii) allowed to adsorb to pre-chilled Vero cells at 4°C for 1 hour, followed by addition of the indicated mAbs at 4°C for 1 hour (post-attachment; open circles). (FIG. 2B) FFWO assay. SL15649 VRPs were adsorbed to pre-chilled Vero cells at 4°C for 1 hour, followed by addition of the mAbs shown (including CHK-152, a positive control murine mAb) for 1 hour. Unbound virus was removed, and cells were exposed to low pH medium (pH 5.5; filled circles) at 37°C for 2 min to trigger viral fusion at the plasma membrane. As a negative control, cells were exposed to neutral pH medium (pH 7.4; open circles) at 37°C for 2 min. For both FIG. 2A and FIG. 2B, cells were incubated at 37°C until 18 hours after infection, and GFP-positive cells were quantified using fluorescence microscopy. The data are combined from two independent experiments, each performed in triplicate.

FIGS. 3A-D. Human mAb therapy against lethal CHIKV infection in *Ifnar*$^{-/-}$ mice. (FIG. 3A) Mice were administered 50 μg of indicated CHIKV-specific or control mAb by intraperitoneal injection 24 hours *before* a lethal challenge of CHIKV (n = 3 to 6 mice per mAb tested). (FIG. 3B) Mice were administered 50 μg of indicated CHIKV-specific or control mAb by intraperitoneal injection 24 hours *after* a lethal challenge of CHIKV (n = 4 to 6 mice per mAb tested). (FIG. 3C) Mice were administered 250 μg of indicated CHIKV-specific or control mAb by intraperitoneal injection 48 hours *after* a lethal challenge of CHIKV (n = 7 to 10 mice per mAb tested). (FIG. 3D) Mice were administered 250 μg of indicated pair of CHIKV-specific mAbs or a control mAb by

intraperitoneal injection 60 hours *after* a lethal challenge of CHIKV (n = 8 mice per mAb combination tested with the exception of 4J21 + 2H1, which is an n = 3). For monotherapy with 4J21 or 4N12, a single dose of 500 μg was given (n = 4 to 5 mice per mAb tested).

FIG. 4. Papular rash at time of acute presentation. The subject presented to the primary care physician with a fever (102°F) of three days duration, with concurrent development of bilateral joint pain in elbows and fingers, and rash. Providers noted a raised, non-pruritic, blanching, papular rash (photograph shown in the figure) across the back, chest and abdomen.

FIG. 5. Identification of mAb competition groups. Quantitative competition binding using Octet-based biolayer interferometry was used to assign mAbs to competition groups. Anti-Penta-His biosensor tips covered with immobilized CHIKV-LR2006 E2 ectodomain were immersed into wells containing primary mAb, followed by immersion into wells containing competing mAbs. The values shown are the percent binding of the competing mAb in the presence of the first mAb (determined by comparing the maximal signal of competing mAb applied after the first mAb complex to the maximal signal of competing mAb alone). MAbs were judged to compete well for binding to the same site if maximum binding of the competing mAb was reduced to <30% of its non-competed binding (black squares) or to exhibit partial completion if the binding of the competing mAb was reduced to < 70% of its non-competed binding (gray squares). MAbs were considered non-competing if maximum binding of the competing mAb was > 70% of its non-competed binding (white squares). Four competition-binding groups were identified, indicated by colored boxes. The corresponding major antigenic sites for mAbs discovered by alanine-scanning mutagenesis (Table 1 and FIGS. 1A-C) are summarized in the columns to the right of the competition matrix. DA indicates domain A; DB indicates domain B, e indicates both arch 1 and 2; NT indicates not tested; NotReact indicates that the mAb did not react against the wild-type envelope proteins; NoReduct indicates the mAb did bind to the wild-type E proteins, but no reduction was noted reproducibly for any mutant. The data are combined from one experiment, with multiple readings for each mAb alone and a single reading of a mAb in combination with each competing antibody.

FIGS. 6A-F. High resolution epitope mapping of CHIKV MAbs. (A) An alanine scanning mutation library for CHIKV envelope protein encompassing 910 E2/E1

mutations was constructed where each amino acid was individually mutated to alanine. Each well of each mutation array plate contains one mutant with a defined substitution. A representative 384-well plate of reactivity results is shown. Eight positive (wild-type E2/E1) and eight negative (mock-transfected) control wells are included on each plate. (B) For epitope mapping, human HEK-293T cells expressing the CHIKV envelope mutation library were tested for immunoreactivity with a MAb of interest (MAb 4G20 shown here) and measured using an Intellicyt high-throughput flow cytometer. Clones with reactivity <30% relative to wild-type CHIKV E2/E1 yet >70% reactivity for a different CHIKV E2/E1 MAb were initially identified as critical for MAb binding. (C) Mutation of four individual residues reduced 4G20 binding (red bars) but did not greatly affect binding of other conformation-dependent MAbs (gray bars) or rabbit polyclonal antibody (rPAb, a gift from IBT Bioservices). Bars represent the mean and range of at least two replicate data points. (D) The epitopes of neutralizing MAbs with PRNT50 < 1,000 ng/ml are mapped onto the trimeric crystal structures of E2/E1 (PDB Entry 2XFC). All neutralizing epitopes map to well-exposed, membrane-distal domains of E2/E1. Each individual E2/E1 heterodimeric subunit is shown in a different color for clarity. Highly immunogenic regions in E2 domains A and B which contain critical epitope residues for multiple MAbs are outlined in red on a single subunit of E2.

FIG. 7. Structural analysis of E2 residues important for mAb binding for antibodies mapped to competition groups. Location of residues required for binding of the human or mouse mAbs from different competition groups (FIGS. 1A-C) mapped onto the crystal structure of E1/E2 (PDB ID 2XFB). A space-filling model of the E1/E2 trimer with E1 colored in white and each E2 monomer colored with light grey, dark grey, or black. The residues required for antibody binding are color-coded according to the competition group(s) to which they belong. Red indicates residues D117 and I121, which are required for binding of 5N23, and belong to competition group 1. Blue indicates residues R80 and G253, which are required for binding by I06 or 5M16, belong to competition group 2. Green indicates residues Q184, S185, I190, V197, R198, Y199, G209, L210, T212, and I217, which are required for binding by CHK-285, CHK-88, or 3A2, and belong to competition group 3. Orange indicates residues H18, which is required for binding of 5F19, and belongs to competition group 4. Purple indicates residues E24, A33, L34, R36, V50, D63, F100, T155, which are required for binding by 5N23, CHK-84, or CHK-141, and belong to competition groups 1 and 2. Teal indicates residues T58, D59, D60, R68, I74, D77, T191, N193, and K234, which are required for

binding by 1H12, and belong to competition groups 2 and 3. Brown indicates residues D71, which is required for binding by CHK-84 and 1H12, and belongs to competition groups 1, 2, and 3. Yellow indicates residues (T58, D71, N72, I74, P75, A76, D77, S118, and R119) that comprise the putative receptor-binding domain (RBD), with the exception of residue D71, which belongs to competition groups 1, 2, and 3. The upper panel shows a bird's eye view of the trimer, the middle panel shows an angled side view of the trimer rotated 45 in the x-axis from the structure in the upper panel, and the bottom panel shows a side view of the trimer rotated 45 in the x-axis from the structure in the middle panel.

FIG. 8. Mechanism of Neutralization by Two Human Anti-CHIKV mAbs, 2H1 or 4N12. Pre- and post-attachment neutralization assays. CHIKV strain SL15649 virus replicon particles (VRPs) were (1) incubated with the mAbs shown (2H1 or 4N12) prior to addition to pre-chilled Vero cells, followed by removal of unbound virus by three washes (pre-attachment; filled circle) or (2) allowed to adsorb to pre-chilled Vero cells followed by addition of the indicated mAbs (post-attachment; open circles). These mAbs neutralized when added prior to or after attachment.

FIG. 9. B6 mouse acute disease model. CHO cell produced recombinant antibodies, given on day 1, reduce virus in ankles compared to control antibody treatment on D+3. Experiments were performed in 4 week-old WT mice after subcutaneous inoculation with 10^3 FFU of CHIKV-LR. Antibodies were given on D+1 and tissues were harvested on D+3 for titration by focus-forming assay.

FIG. 10. B6 mouse acute disease model. CHKV mAb 4N12 produced in CHO cells, given systemically on day 3, reduces virus titer in ankles Experiments were performed in 4 week-old WT mice after subcutaneous inoculation with 10e3 FFU of CHIKV-LR. Antibodies were given on D+3 and tissues were harvested on D+5 for titration by focus-forming assay.

FIG. 11. B6 mouse chronic disease model. CHKV mAbs produced in CHO cells, given systemically on day 3, reduces virus genomic equivalents, on day 28, in ankles. Experiments were performed in 4 week-old WT mice after inoculation with 10e3 FFU of CHIKV-LR. Antibodies (300 μg) were given on D+3 and tissues were harvested on D+28 for analysis by qRT-PCR.

FIG. 12. INFNAR knockout lethal disease mouse model. CHKV mAbs produced in CHO cells, given systemically at 60 hours post-infection, enhance survival. Experiments were performed in 4-5 week-old IFNAR-/- mice after subcutaneous

inoculation with 10e3 FFU of CHIKV-LR. Antibodies were given 60 hours after infection and mortality was followed for 21 days.

FIG. 13. Neutralization curves for hybridoma-produced ('old') or recombinant ('new') CHIKV-specific mAbs. Neutralization curves were performed in BHK21 cells. 100 FFU of CHIKV-LR was mixed with indicated mAbs for 1 h at 37 °C prior to addition to BHK21 cells. Infection was determined by a focus forming assay.

FIG. 14. Half maximal effective inhibitory concentration (EC_{50}; ng/mL) for hybridoma-produced versus recombinant CHO cell-produced antibodies. Data are similar for hybridoma-produced versus recombinant.

FIG. 15. Alignments of both the E1 and E2 proteins as amino acids, and the nucleotides for the genes that encode the proteins. Genbank accession number for proteins is listed with the virus strain. Three strains for viruses from the prototypic groups: East.Central.South Africa (ECSA), two for Asian, and the one West African strain are provided. These antibodies cross react across all strains.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The inventors isolated a large panel of human mAbs that neutralize CHIKV infectivity in cell culture and successfully treated *Ifnar*$^{-/-}$mice (lacking type I interferon receptors) inoculated with a lethal dose of CHIKV, even when administered as late as 60 hours after infection. They identified the A domain of E2 as the major antigenic site for recognition by mAbs that broadly neutralize CHIKV infection with ultrapotent activity and showed that the principal mechanism of inhibition is to prevent fusion. These and other aspects of the disclosure are described in detail below.

I. Chikungunya and Chikungunya Virus

Chikungunya is an infection caused by the chikungunya virus. It features sudden onset fever usually lasting two to seven days, and joint pains typically lasting weeks or months but sometimes years. The mortality rate is a little less than 1 in 1000, with the elderly most likely to die. The virus is passed to humans by two species of mosquito of the genus *Aedes*: *A. albopictus* and *A. aegypti*. Animal reservoirs of the virus include monkeys, birds, cattle, and rodents. This is in contrast to dengue, for which only primates are hosts.

The best means of prevention is overall mosquito control and the avoidance of bites by any infected mosquitoes. No specific treatment is known, but medications can be used to reduce symptoms. Rest and fluids may also be useful.

The incubation period of chikungunya disease ranges from two to twelve days, typically three to seven. Between 72 and 97% of those infected will develop symptoms. Symptoms include sudden onset, sometimes biphasic fever typically lasting from a few days to a week, sometimes up to ten days, usually above 39 °C (102 °F) and sometimes reaching 41 °C (104 °F), and strong joint pain or stiffness usually lasting weeks or months but sometimes lasting years. Rash (usually maculopapular), muscle pain, headache, fatigue, nausea or vomiting may also be present. Inflammation of the eyes may present as iridocyclitis, or uveitis, and retina lesions may occur. Typically, the fever lasts for two days and then ends abruptly. However, headache, insomnia and an extreme degree of prostration last for a variable period, usually about five to seven days.

Observations during recent epidemics have suggested chikungunya may cause long-term symptoms following acute infection. During the La Reunion outbreak in 2006, more than 50% of subjects over the age of 45 reported long-term musculoskeletal pain with up to 60% of people reporting prolonged painful joints three years following initial infection. A

study of imported cases in France reported that 59% of people still suffered from arthralgia two years after acute infection. Following a local epidemic of chikungunya in Italy, 66% of people reported muscle pains, joint pains, or asthenia at one year after acute infection. Long-term symptoms are not an entirely new observation; long-term arthritis was observed following an outbreak in 1979. Common predictors of prolonged symptoms are increased age and prior rheumatological disease. The cause of these chronic symptoms is currently not fully known. Markers of autoimmune or rheumatoid disease have not been found in people reporting chronic symptoms. However, some evidence from humans and animal models suggests chikungunya may be able to establish chronic infections within the host. Viral antigen was detected in a muscle biopsy of a people suffering a recurrent episode of disease three months after initial onset. Additionally, viral antigen and RNA were found in synovial macrophages of a person during a relapse of musculoskeletal disease 18 months after initial infection. Several animal models have also suggested chikungunya virus may establish persistent infections. In a mouse model, viral RNA was detected specifically in joint-associated tissue for at least 16 weeks after inoculation, and was associated with chronic synovitis. Similarly, another study reported detection of a viral reporter gene in joint tissue of mice for weeks after inoculation. In a non-human primate model, chikungunya virus was found to persist in the spleen for at least six weeks.

Chikungunya virus is an alphavirus with a positive-sense single-stranded RNA genome of about 11.6kb. It is a member of the Semliki Forest virus complex and is closely related to Ross River virus, O'nyong'nyong virus, and Semliki Forest virus. In the United States, it is classified as a category C priority pathogen and work requires biosafety level III precautions. Human epithelial and endothelial cells, primary fibroblasts, and monocyte-derived macrophages are permissive for chikungunya virus *in vitro*, and viral replication is highly cytopathic, but susceptible to type-I and -II interferon. *In vivo*, chikungunya virus appears to replicate in fibroblasts, skeletal muscle progenitor cells, and myofibers.

Chikungunya virus is an alphavirus, as are the viruses that cause eastern equine encephalitis and western equine encephalitis. Chikungunya is generally spread through bites from *A. aegypti* mosquitoes, but recent research by the Pasteur Institute in Paris has suggested chikungunya virus strains in the 2005-2006 Reunion Island outbreak incurred a mutation that facilitated transmission by the Asian tiger mosquito (*A. albopictus*).

Chikungunya virus infection of *A. albopictus* was caused by a point mutation in one of the viral envelope genes (*E1*). Enhanced transmission of chikungunya virus by *A. albopictus* could mean an increased risk for outbreaks in other areas where the Asian tiger

mosquito is present. A recent epidemic in Italy was likely perpetuated by *A. albopictus*. In Africa, chikungunya is spread by a sylvatic cycle in which the virus largely resides in other primates between human outbreaks.

Upon infection with chikungunya, the host's fibroblasts produce type-1 (alpha and beta) interferon. Mice that lack the interferon alpha receptor die in two to three days upon being exposed to 10^2 chikungunya PFUs, while wild-type mice survive even when exposed to as many as 10^6 PFUs of the virus. At the same time, mice that are partially type-1 deficient (IFN α/β +/−) are mildly affected and experience symptoms such as muscle weakness and lethargy. Partidos *et al.* (2011) saw similar results with the live attenuated strain CHIKV181/25. However, rather than dying, the type-1 interferon-deficient (IFN α/β −/−) mice were temporarily disabled and the partially type-1 interferon-deficient mice did not have any problems.

Several studies have attempted to find the upstream components of the type-1 interferon pathway involved in the host's response to chikungunya infection. So far, no one knows the chikungunya-specific pathogen associated molecular pattern. Nonetheless, IPS-1—also known as Cardif, MAVS, and VISA—has been found to be an important factor. In 2011, White et al. found that interfering with IPS-1 decreased the phosphorylation of interferon regulatory factor 3 (IRF3) and the production of IFN-β. Other studies have found that IRF3 and IRF7 are important in an age-dependent manner. Adult mice that lack both of these regulatory factors die upon infection with chikungunya. Neonates, on the other hand, succumb to the virus if they are deficient in one of these factors.

Chikungunya counters the type-I interferon response by producing NS2, a nonstructural protein that degrades RBP1 and turns off the host cell's ability to transcribe DNA. NS2 interferes with the JAK-STAT signaling pathway and prevents STAT from becoming phosphorylated.

Common laboratory tests for chikungunya include RT-PCR, virus isolation, and serological tests. Virus isolation provides the most definitive diagnosis, but takes one to two weeks for completion and must be carried out in biosafety level III laboratories. The technique involves exposing specific cell lines to samples from whole blood and identifying chikungunya virus-specific responses. RT-PCR using nested primer pairs is used to amplify several chikungunya-specific genes from whole blood. Results can be determined in one to two days.

Serological diagnosis requires a larger amount of blood than the other methods, and uses an ELISA assay to measure chikungunya-specific IgM levels. Results require two to

three days, and false positives can occur with infection via other related viruses, such as o'nyong'nyong virus and Semliki Forest virus.

The differential diagnosis may include infection with other mosquito-borne viruses, such as dengue, and influenza. Chronic recurrent polyarthralgia occurs in at least 20% of chikungunya patients one year after infection, whereas such symptoms are uncommon in dengue.

Currently, no specific treatment is available. Attempts to relieve the symptoms include the use of NSAIDs such as naproxen or paracetamol (acetaminophen) and fluids. Aspirin is not recommended. In those who have more than two weeks of arthritis, ribavirin may be useful. The effect of chloroquine is not clear. It does not appear to help acute disease, but tentative evidence indicates it might help those with chronic arthritis. Steroids do not appear useful, either.

Chikungunya is mostly present in the developing world. The epidemiology of chikungunya is related to mosquitoes, their environments, and human behavior. The adaptation of mosquitoes to the changing climate of North Africa around 5,000 years ago made them seek out environments where humans stored water. Human habitation and the mosquitoes' environments were then very closely connected. During periods of epidemics humans are the reservoir of the virus. During other times, monkey, birds and other vertebrates have served as reservoirs.

Three genotypes of this virus have been described: West African, East/Central/South African, and Asian genotypes. Explosive epidemics in Indian Ocean in 2005 and Pacific Islands in 2011, as well as now in the Americas, continue to change the distribution of genotypes.

On 28 May 2009 in Changwat Trang of Thailand, where the virus is endemic, the provincial hospital decided to deliver by Caesarean section a male baby from his chikungunya-infected mother, Khwanruethai Sutmueang, 28, a Trang native, to prevent mother-fetus virus transmission. However, after delivering the baby, the physicians discovered the baby was already infected with the virus, and put him into intensive care because the infection had left the baby unable to breathe by himself or to drink milk. The physicians presumed the virus might be able to be transmitted from a mother to her fetus, but without laboratory confirmation.

In December 2013, chikungunya was confirmed on the Caribbean island of St. Martin with 66 confirmed cases and suspected cases of around 181. This outbreak is the first time in the Western Hemisphere that the disease has spread to humans from a population of infected

mosquitoes. By January 2014, the Public Health Agency of Canada reported that cases were confirmed on the British Virgin Islands, Saint-Barthélemy, Guadeloupe, Dominica, Martinique, and French Guyana. In April 2014, chikungunya was also confirmed in the Dominican Republic by the Centers for Disease Control and Prevention (CDC). By the end of April, it had spread to 14 countries in all, including Jamaica, St. Lucia, St. Kitts and Nevis, and Haiti where an epidemic was declared.

By the end of May 2014, over ten imported cases of the virus had been reported in the United States by people traveling to Florida from areas where the virus is endemic. The strain of chikungunya spreading to the U.S. from the Caribbean is most easily spread by *A. aegypti*. Concern exists that this strain of chikungunya could mutate to make the *A. albopictus* vector more efficient. If this mutation were to occur, chikungunya would be more of a public health concern to the US because the *A. albopictus* or Asian tiger mosquito is more widespread in the U.S. and is more aggressive than the *A. aegypti*.

On June 2014 six cases of the virus were confirmed in Brazil, two in the city of Campinas in the state of São Paulo. The six cases are Brazilian army soldiers who had recently returned from Haiti, where they were participating in the reconstruction efforts as members of the United Nations Stabilisation Mission in Haiti. The information was officially released by Campinas municipality, which considers that it has taken the appropriate actions.

On 16 June 2014, Florida had a cumulative total of 42 cases. As of 11 September 2014, the number of reported cases in Puerto Rico for the year was 1,636. By 28 October, that number had increased to 2,974 confirmed cases with over 10,000 cases suspected. On 17 June 2014, Department of Health officials in the U.S. state of Mississippi confirmed they are investigating the first potential case in a Mississippi resident who recently travelled to Haiti. On 19 June 2014, the virus had spread to Georgia, USA. On 24 June 2014, a case was reported in Poinciana, Polk County, Florida, USA. On 25 June 2014, the Health Department of the U.S. state of Arkansas confirmed that one person from that state is carrying chikungunya. On 26 June 2014, a case was reported in the Mexican state of Jalisco.

On 17 July 2014, the first chikungunya case acquired in the United States was reported in Florida by the Centers for Disease Control and Prevention. Since 2006, over 200 cases have been reported in the United States, but only in people who had traveled to other countries. This is the first time the virus was passed by mosquitoes to a person on the U.S. mainland. On 2 September 2014, the Centers for Disease Control and Prevention reported that there had been seven confirmed cases of chikungunya in the United States in people who had acquired the disease locally.

On 25 September 2014, official authorities in El Salvador report over 30,000 confirmed cases of this new epidemy. The new epidemic is also on the rise in Jamaica and in Barbados. There is a risk that tourists to those countries may bring the virus to their own countries. Nov 2014: Brazil has reported a local transmission of a different strain (genotype) of chikungunya that has never been documented in the Americas. This is an African genotype, but oddly fails to explain if it is South African or West African. The new genotype (in the Americas) is more severe than the Asian genotype which is currently spreading through the Americas, and immunity to one genotype does not confer immunity to others. French Polynesia is among other regions experiencing ongoing outbreaks.

On 7 November 2014 Mexico reported an outbreak of chikungunya, acquired by local transmission, in southern state of Chiapas. The outbreak extends across the coastline from the Guatemala border to the neighbouring state of Oaxaca. Health authorities have reported a cumulative load of 39 laboratory-confirmed cases (by the end of week 48). No suspect cases have been reported. In January 2015, there were 90,481 reported cases of chikungunya in Colombia.

II. Monoclonal Antibodies and Production Thereof

A. General Methods

It will be understood that monoclonal antibodies binding to Chikungunya virus will have several applications. These include the production of diagnostic kits for use in detecting and diagnosing Chikungunya virus infection, as well as for treating the same. In these contexts, one may link such antibodies to diagnostic or therapeutic agents, use them as capture agents or competitors in competitive assays, or use them individually without additional agents being attached thereto. The antibodies may be mutated or modified, as discussed further below. Methods for preparing and characterizing antibodies are well known in the art (see, *e.g.*, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988; U.S. Patent 4,196,265).

The methods for generating monoclonal antibodies (MAbs) generally begin along the same lines as those for preparing polyclonal antibodies. The first step for both these methods is immunization of an appropriate host or identification of subjects who are immune due to prior natural infection. As is well known in the art, a given composition for immunization may vary in its immunogenicity. It is often necessary therefore to boost the host immune system, as may be achieved by coupling a peptide or polypeptide immunogen to a carrier. Exemplary and preferred carriers are keyhole limpet hemocyanin (KLH) and bovine serum

albumin (BSA). Other albumins such as ovalbumin, mouse serum albumin or rabbit serum albumin can also be used as carriers. Means for conjugating a polypeptide to a carrier protein are well known in the art and include glutaraldehyde, m-maleimidobencoyl-N-hydroxysuccinimide ester, carbodiimyde and bis-biazotized benzidine. As also is well known in the art, the immunogenicity of a particular immunogen composition can be enhanced by the use of non-specific stimulators of the immune response, known as adjuvants. Exemplary and preferred adjuvants include complete Freund's adjuvant (a non-specific stimulator of the immune response containing killed *Mycobacterium tuberculosis)*, incomplete Freund's adjuvants and aluminum hydroxide adjuvant.

The amount of immunogen composition used in the production of polyclonal antibodies varies upon the nature of the immunogen as well as the animal used for immunization. A variety of routes can be used to administer the immunogen (subcutaneous, intramuscular, intradermal, intravenous and intraperitoneal). The production of polyclonal antibodies may be monitored by sampling blood of the immunized animal at various points following immunization. A second, booster injection, also may be given. The process of boosting and titering is repeated until a suitable titer is achieved. When a desired level of immunogenicity is obtained, the immunized animal can be bled and the serum isolated and stored, and/or the animal can be used to generate MAbs.

Following immunization, somatic cells with the potential for producing antibodies, specifically B lymphocytes (B cells), are selected for use in the MAb generating protocol. These cells may be obtained from biopsied spleens or lymph nodes, or from circulating blood. The antibody-producing B lymphocytes from the immunized animal are then fused with cells of an immortal myeloma cell, generally one of the same species as the animal that was immunized or human or human/mouse chimeric cells. Myeloma cell lines suited for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render then incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas). Any one of a number of myeloma cells may be used, as are known to those of skill in the art (Goding, pp. 65-66, 1986; Campbell, pp. 75-83, 1984).

Methods for generating hybrids of antibody-producing spleen or lymph node cells and myeloma cells usually comprise mixing somatic cells with myeloma cells in a 2:1 proportion, though the proportion may vary from about 20:1 to about 1:1, respectively, in the presence of an agent or agents (chemical or electrical) that promote the fusion of cell membranes. Fusion methods using Sendai virus have been described by Kohler and Milstein (1975; 1976), and

those using polyethylene glycol (PEG), such as 37% (v/v) PEG, by Gefter *et al.* (1977). The use of electrically induced fusion methods also is appropriate (Goding, pp. 71-74, 1986). Fusion procedures usually produce viable hybrids at low frequencies, about 1 x 10^{-6} to 1 x 10^{-8}. However, this does not pose a problem, as the viable, fused hybrids are differentiated from the parental, infused cells (particularly the infused myeloma cells that would normally continue to divide indefinitely) by culturing in a selective medium. The selective medium is generally one that contains an agent that blocks the *de novo* synthesis of nucleotides in the tissue culture media. Exemplary and preferred agents are aminopterin, methotrexate, and azaserine. Aminopterin and methotrexate block *de novo* synthesis of both purines and pyrimidines, whereas azaserine blocks only purine synthesis. Where aminopterin or methotrexate is used, the media is supplemented with hypoxanthine and thymidine as a source of nucleotides (HAT medium). Where azaserine is used, the media is supplemented with hypoxanthine. Ouabain is added if the B cell source is an Epstein Barr virus (EBV) transformed human B cell line, in order to eliminate EBV transformed lines that have not fused to the myeloma.

The preferred selection medium is HAT or HAT with ouabain. Only cells capable of operating nucleotide salvage pathways are able to survive in HAT medium. The myeloma cells are defective in key enzymes of the salvage pathway, *e.g.*, hypoxanthine phosphoribosyl transferase (HPRT), and they cannot survive. The B cells can operate this pathway, but they have a limited life span in culture and generally die within about two weeks. Therefore, the only cells that can survive in the selective media are those hybrids formed from myeloma and B cells. When the source of B cells used for fusion is a line of EBV-transformed B cells, as here, ouabain may also be used for drug selection of hybrids as EBV-transformed B cells are susceptible to drug killing, whereas the myeloma partner used is chosen to be ouabain resistant.

Culturing provides a population of hybridomas from which specific hybridomas are selected. Typically, selection of hybridomas is performed by culturing the cells by single-clone dilution in microtiter plates, followed by testing the individual clonal supernatants (after about two to three weeks) for the desired reactivity. The assay should be sensitive, simple and rapid, such as radioimmunoassays, enzyme immunoassays, cytotoxicity assays, plaque assays dot immunobinding assays, and the like. The selected hybridomas are then serially diluted or single-cell sorted by flow cytometric sorting and cloned into individual antibody-producing cell lines, which clones can then be propagated indefinitely to provide mAbs. The cell lines may be exploited for MAb production in two basic ways. A sample of

the hybridoma can be injected (often into the peritoneal cavity) into an animal (*e.g.*, a mouse). Optionally, the animals are primed with a hydrocarbon, especially oils such as pristane (tetramethylpentadecane) prior to injection. When human hybridomas are used in this way, it is optimal to inject immunocompromised mice, such as SCID mice, to prevent tumor rejection. The injected animal develops tumors secreting the specific monoclonal antibody produced by the fused cell hybrid. The body fluids of the animal, such as serum or ascites fluid, can then be tapped to provide MAbs in high concentration. The individual cell lines could also be cultured *in vitro*, where the MAbs are naturally secreted into the culture medium from which they can be readily obtained in high concentrations. Alternatively, human hybridoma cells lines can be used *in vitro* to produce immunoglobulins in cell supernatant. The cell lines can be adapted for growth in serum-free medium to optimize the ability to recover human monoclonal immunoglobulins of high purity.

MAbs produced by either means may be further purified, if desired, using filtration, centrifugation and various chromatographic methods such as FPLC or affinity chromatography. Fragments of the monoclonal antibodies of the disclosure can be obtained from the purified monoclonal antibodies by methods which include digestion with enzymes, such as pepsin or papain, and/or by cleavage of disulfide bonds by chemical reduction. Alternatively, monoclonal antibody fragments encompassed by the present disclosure can be synthesized using an automated peptide synthesizer.

It also is contemplated that a molecular cloning approach may be used to generate monoclonals. For this, RNA can be isolated from the hybridoma line and the antibody genes obtained by RT-PCR and cloned into an immunoglobulin expression vector. Alternatively, combinatorial immunoglobulin phagemid libraries are prepared from RNA isolated from the cell lines and phagemids expressing appropriate antibodies are selected by panning using viral antigens. The advantages of this approach over conventional hybridoma techniques are that approximately 10^4 times as many antibodies can be produced and screened in a single round, and that new specificities are generated by H and L chain combination which further increases the chance of finding appropriate antibodies.

Other U.S. patents, each incorporated herein by reference, that teach the production of antibodies useful in the present disclosure include U.S. Patent 5,565,332, which describes the production of chimeric antibodies using a combinatorial approach; U.S. Patent 4,816,567 which describes recombinant immunoglobulin preparations; and U.S. Patent 4,867,973 which describes antibody-therapeutic agent conjugates.

B. Antibodies of the Present Disclosure

Antibodies according to the present disclosure may be defined, in the first instance, by their binding specificity, which in this case is for Chikungunya virus glycoprotein (GP). Those of skill in the art, by assessing the binding specificity/affinity of a given antibody using techniques well known to those of skill in the art, can determine whether such antibodies fall within the scope of the instant claims. In one aspect, there are provided monoclonal antibodies having clone-paired CDR's from the heavy and light chains as illustrated in Tables 3 and 4, respectively. Such antibodies may be produced by the clones discussed below in the Examples section using methods described herein.

In a second aspect, the antibodies may be defined by their variable sequence, which include additional "framework" regions. These are provided in Tables 1 and 2 that encode or represent full variable regions. Furthermore, the antibodies sequences may vary from these sequences, optionally using methods discussed in greater detail below. For example, nucleic acid sequences may vary from those set out above in that (a) the variable regions may be segregated away from the constant domains of the light and heavy chains, (b) the nucleic acids may vary from those set out above while not affecting the residues encoded thereby, (c) the nucleic acids may vary from those set out above by a given percentage, *e.g.*, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homology, (d) the nucleic acids may vary from those set out above by virtue of the ability to hybridize under high stringency conditions, as exemplified by low salt and/or high temperature conditions, such as provided by about 0.02 M to about 0.15 M NaCl at temperatures of about 50°C to about 70°C, (e) the amino acids may vary from those set out above by a given percentage, *e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homology, or (f) the amino acids may vary from those set out above by permitting conservative substitutions (discussed below). Each of the foregoing applies to the nucleic acid sequences set forth as Table 1 and the amino acid sequences of Table 2.

C. Engineering of Antibody Sequences

In various embodiments, one may choose to engineer sequences of the identified antibodies for a variety of reasons, such as improved expression, improved cross-reactivity or diminished off-target binding. The following is a general discussion of relevant techniques for antibody engineering.

Hybridomas may be cultured, then cells lysed, and total RNA extracted. Random hexamers may be used with RT to generate cDNA copies of RNA, and then PCR performed

using a multiplex mixture of PCR primers expected to amplify all human variable gene sequences. PCR product can be cloned into pGEM-T Easy vector, then sequenced by automated DNA sequencing using standard vector primers. Assay of binding and neutralization may be performed using antibodies collected from hybridoma supernatants and purified by FPLC, using Protein G columns.

Recombinant full length IgG antibodies were generated by subcloning heavy and light chain Fv DNAs from the cloning vector into an IgG plasmid vector, transfected into 293 Freestyle cells or CHO cells, and antibodies were collected an purified from the 293 or CHO cell supernatant.

The rapid availability of antibody produced in the same host cell and cell culture process as the final cGMP manufacturing process has the potential to reduce the duration of process development programs. Lonza has developed a generic method using pooled transfectants grown in CDACF medium, for the rapid production of small quantities (up to 50 g) of antibodies in CHO cells. Although slightly slower than a true transient system, the advantages include a higher product concentration and use of the same host and process as the production cell line. Example of growth and productivity of GS-CHO pools, expressing a model antibody, in a disposable bioreactor: in a disposable bag bioreactor culture (5 L working volume) operated in fed-batch mode, a harvest antibody concentration of 2 g/L was achieved within 9 weeks of transfection.

Antibody molecules will comprise fragments (such as F(ab'), $F(ab')_2$) that are produced, for example, by the proteolytic cleavage of the mAbs, or single-chain immunoglobulins producible, for example, via recombinant means. Such antibody derivatives are monovalent. In one embodiment, such fragments can be combined with one another, or with other antibody fragments or receptor ligands to form "chimeric" binding molecules. Significantly, such chimeric molecules may contain substituents capable of binding to different epitopes of the same molecule.

In related embodiments, the antibody is a derivative of the disclosed antibodies, *e.g.*, an antibody comprising the CDR sequences identical to those in the disclosed antibodies (*e.g.*, a chimeric, or CDR-grafted antibody). Alternatively, one may wish to make modifications, such as introducing conservative changes into an antibody molecule. In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein,

which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like.

It also is understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U.S. Patent 4,554,101, incorporated herein by reference, states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein. As detailed in U.S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: basic amino acids: arginine (+3.0), lysine (+3.0), and histidine (-0.5); acidic amino acids: aspartate (+3.0 ± 1), glutamate (+3.0 ± 1), asparagine (+0.2), and glutamine (+0.2); hydrophilic, nonionic amino acids: serine (+0.3), asparagine (+0.2), glutamine (+0.2), and threonine (-0.4), sulfur containing amino acids: cysteine (-1.0) and methionine (-1.3); hydrophobic, nonaromatic amino acids: valine (-1.5), leucine (-1.8), isoleucine (-1.8), proline (-0.5 ± 1), alanine (-0.5), and glycine (0); hydrophobic, aromatic amino acids: tryptophan (-3.4), phenylalanine (-2.5), and tyrosine (-2.3).

It is understood that an amino acid can be substituted for another having a similar hydrophilicity and produce a biologically or immunologically modified protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ± 2 is preferred, those that are within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

As outlined above, amino acid substitutions generally are based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take into consideration the various foregoing characteristics are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

The present disclosure also contemplates isotype modification. By modifying the Fc region to have a different isotype, different functionalities can be achieved. For example, changing to IgG_1 can increase antibody dependent cell cytotoxicity, switching to class A can improve tissue distribution, and switching to class M can improve valency.

Modified antibodies may be made by any technique known to those of skill in the art, including expression through standard molecular biological techniques, or the chemical synthesis of polypeptides. Methods for recombinant expression are addressed elsewhere in this document.

D. Single Chain Antibodies

A Single Chain Variable Fragment (scFv) is a fusion of the variable regions of the heavy and light chains of immunoglobulins, linked together with a short (usually serine, glycine) linker. This chimeric molecule retains the specificity of the original immunoglobulin, despite removal of the constant regions and the introduction of a linker peptide. This modification usually leaves the specificity unaltered. These molecules were created historically to facilitate phage display where it is highly convenient to express the antigen binding domain as a single peptide. Alternatively, scFv can be created directly from subcloned heavy and light chains derived from a hybridoma. Single chain variable fragments lack the constant Fc region found in complete antibody molecules, and thus, the common binding sites (*e.g.*, protein A/G) used to purify antibodies. These fragments can often be purified/immobilized using Protein L since Protein L interacts with the variable region of kappa light chains.

Flexible linkers generally are comprised of helix- and turn-promoting amino acid residues such as alaine, serine and glycine. However, other residues can function as well. Tang *et al.* (1996) used phage display as a means of rapidly selecting tailored linkers for single-chain antibodies (scFvs) from protein linker libraries. A random linker library was constructed in which the genes for the heavy and light chain variable domains were linked by a segment encoding an 18-amino acid polypeptide of variable composition. The scFv repertoire (approx. 5×10^6 different members) was displayed on filamentous phage and subjected to affinity selection with hapten. The population of selected variants exhibited significant increases in binding activity but retained considerable sequence diversity. Screening 1054 individual variants subsequently yielded a catalytically active scFv that was produced efficiently in soluble form. Sequence analysis revealed a conserved proline in the linker two residues after the V_H C terminus and an abundance of arginines and prolines at other positions as the only common features of the selected tethers.

The recombinant antibodies of the present disclosure may also involve sequences or moieties that permit dimerization or multimerization of the receptors. Such sequences include those derived from IgA, which permit formation of multimers in conjunction with the J-chain. Another multimerization domain is the Gal4 dimerization domain. In other embodiments, the chains may be modified with agents such as biotin/avidin, which permit the combination of two antibodies.

In a separate embodiment, a single-chain antibody can be created by joining receptor light and heavy chains using a non-peptide linker or chemical unit. Generally, the light and

heavy chains will be produced in distinct cells, purified, and subsequently linked together in an appropriate fashion (*i.e.*, the N-terminus of the heavy chain being attached to the C-terminus of the light chain via an appropriate chemical bridge).

Cross-linking reagents are used to form molecular bridges that tie functional groups of two different molecules, *e.g.*, a stablizing and coagulating agent. However, it is contemplated that dimers or multimers of the same analog or heteromeric complexes comprised of different analogs can be created. To link two different compounds in a step-wise manner, hetero-bifunctional cross-linkers can be used that eliminate unwanted homopolymer formation.

An exemplary hetero-bifunctional cross-linker contains two reactive groups: one reacting with primary amine group (*e.g.*, N-hydroxy succinimide) and the other reacting with a thiol group (*e.g.*, pyridyl disulfide, maleimides, halogens, *etc.*). Through the primary amine reactive group, the cross-linker may react with the lysine residue(s) of one protein (*e.g.*, the selected antibody or fragment) and through the thiol reactive group, the cross-linker, already tied up to the first protein, reacts with the cysteine residue (free sulfhydryl group) of the other protein (*e.g.*, the selective agent).

It is preferred that a cross-linker having reasonable stability in blood will be employed. Numerous types of disulfide-bond containing linkers are known that can be successfully employed to conjugate targeting and therapeutic/preventative agents. Linkers that contain a disulfide bond that is sterically hindered may prove to give greater stability *in vivo*, preventing release of the targeting peptide prior to reaching the site of action. These linkers are thus one group of linking agents.

Another cross-linking reagent is SMPT, which is a bifunctional cross-linker containing a disulfide bond that is "sterically hindered" by an adjacent benzene ring and methyl groups. It is believed that steric hindrance of the disulfide bond serves a function of protecting the bond from attack by thiolate anions such as glutathione which can be present in tissues and blood, and thereby help in preventing decoupling of the conjugate prior to the delivery of the attached agent to the target site.

The SMPT cross-linking reagent, as with many other known cross-linking reagents, lends the ability to cross-link functional groups such as the SH of cysteine or primary amines (*e.g.*, the epsilon amino group of lysine). Another possible type of cross-linker includes the hetero-bifunctional photoreactive phenylazides containing a cleavable disulfide bond such as sulfosuccinimidyl-2-(p-azido salicylamido) ethyl-1,3'-dithiopropionate. The N-hydroxy-succinimidyl group reacts with primary amino groups and the phenylazide (upon photolysis) reacts non-selectively with any amino acid residue.

In addition to hindered cross-linkers, non-hindered linkers also can be employed in accordance herewith. Other useful cross-linkers, not considered to contain or generate a protected disulfide, include SATA, SPDP and 2-iminothiolane (Wawrzynczak & Thorpe, 1987). The use of such cross-linkers is well understood in the art. Another embodiment involves the use of flexible linkers.

U.S. Patent 4,680,338, describes bifunctional linkers useful for producing conjugates of ligands with amine-containing polymers and/or proteins, especially for forming antibody conjugates with chelators, drugs, enzymes, detectable labels and the like. U.S. Patents 5,141,648 and 5,563,250 disclose cleavable conjugates containing a labile bond that is cleavable under a variety of mild conditions. This linker is particularly useful in that the agent of interest may be bonded directly to the linker, with cleavage resulting in release of the active agent. Particular uses include adding a free amino or free sulfhydryl group to a protein, such as an antibody, or a drug.

U.S. Patent 5,856,456 provides peptide linkers for use in connecting polypeptide constituents to make fusion proteins, *e.g.*, single chain antibodies. The linker is up to about 50 amino acids in length, contains at least one occurrence of a charged amino acid (preferably arginine or lysine) followed by a proline, and is characterized by greater stability and reduced aggregation. U.S. Patent 5,880,270 discloses aminooxy-containing linkers useful in a variety of immunodiagnostic and separative techniques.

E. Intrabodies

In a particular embodiment, the antibody is a recombinant antibody that is suitable for action inside of a cell – such antibodies are known as "intrabodies." These antibodies may interfere with target function by a variety of mechanism, such as by altering intracellular protein trafficking, interfering with enzymatic function, and blocking protein-protein or protein-DNA interactions. In many ways, their structures mimic or parallel those of single chain and single domain antibodies, discussed above. Indeed, single-transcript/single-chain is an important feature that permits intracellular expression in a target cell, and also makes protein transit across cell membranes more feasible. However, additional features are required.

The two major issues impacting the implementation of intrabody therapeutic are delivery, including cell/tissue targeting, and stability. With respect to delivery, a variety of approaches have been employed, such as tissue-directed delivery, use of cell-type specific promoters, viral-based delivery and use of cell-permeability/membrane translocating peptides.

With respect to the stability, the approach is generally to either screen by brute force, including methods that involve phage diplay and may include sequence maturation or development of consensus sequences, or more directed modifications such as insertion stabilizing sequences (*e.g.*, Fc regions, chaperone protein sequences, leucine zippers) and disulfide replacement/modification.

An additional feature that intrabodies may require is a signal for intracellular targeting. Vectors that can target intrabodies (or other proteins) to subcellular regions such as the cytoplasm, nucleus, mitochondria and ER have been designed and are commercially available (Invitrogen Corp.; Persic *et al.*, 1997).

By virtue of their ability to enter cells, intrabodies have additional uses that other types of antibodies may not achieve. In the case of the present antibodies, the ability to interact with the MUC1 cytoplasmic domain in a living cell may interfere with functions associated with the MUC1 CD, such as signaling functions (binding to other molecules) or oligomer formation. In particular, it is contemplated that such antibodies can be used to inhibit MUC1 dimer formation.

F. Purification

In certain embodiments, the antibodies of the present disclosure may be purified. The term "purified," as used herein, is intended to refer to a composition, isolatable from other components, wherein the protein is purified to any degree relative to its naturally-obtainable state. A purified protein therefore also refers to a protein, free from the environment in which it may naturally occur. Where the term "substantially purified" is used, this designation will refer to a composition in which the protein or peptide forms the major component of the composition, such as constituting about 50%, about 60%, about 70%, about 80%, about 90%, about 95% or more of the proteins in the composition.

Protein purification techniques are well known to those of skill in the art. These techniques involve, at one level, the crude fractionation of the cellular milieu to polypeptide and non-polypeptide fractions. Having separated the polypeptide from other proteins, the polypeptide of interest may be further purified using chromatographic and electrophoretic techniques to achieve partial or complete purification (or purification to homogeneity). Analytical methods particularly suited to the preparation of a pure peptide are ion-exchange chromatography, exclusion chromatography; polyacrylamide gel electrophoresis; isoelectric focusing. Other methods for protein purification include, precipitation with ammonium sulfate, PEG, antibodies and the like or by heat denaturation, followed by centrifugation; gel

filtration, reverse phase, hydroxylapatite and affinity chromatography; and combinations of such and other techniques.

In purifying an antibody of the present disclosure, it may be desirable to express the polypeptide in a prokaryotic or eukaryotic expression system and extract the protein using denaturing conditions. The polypeptide may be purified from other cellular components using an affinity column, which binds to a tagged portion of the polypeptide. As is generally known in the art, it is believed that the order of conducting the various purification steps may be changed, or that certain steps may be omitted, and still result in a suitable method for the preparation of a substantially purified protein or peptide.

Commonly, complete antibodies are fractionated utilizing agents (*i.e.*, protein A) that bind the Fc portion of the antibody. Alternatively, antigens may be used to simultaneously purify and select appropriate antibodies. Such methods often utilize the selection agent bound to a support, such as a column, filter or bead. The antibodies is bound to a support, contaminants removed (*e.g.*, washed away), and the antibodies released by applying conditions (salt, heat, *etc.*).

Various methods for quantifying the degree of purification of the protein or peptide will be known to those of skill in the art in light of the present disclosure. These include, for example, determining the specific activity of an active fraction, or assessing the amount of polypeptides within a fraction by SDS/PAGE analysis. Another method for assessing the purity of a fraction is to calculate the specific activity of the fraction, to compare it to the specific activity of the initial extract, and to thus calculate the degree of purity. The actual units used to represent the amount of activity will, of course, be dependent upon the particular assay technique chosen to follow the purification and whether or not the expressed protein or peptide exhibits a detectable activity.

It is known that the migration of a polypeptide can vary, sometimes significantly, with different conditions of SDS/PAGE (Capaldi *et al.*, 1977). It will therefore be appreciated that under differing electrophoresis conditions, the apparent molecular weights of purified or partially purified expression products may vary.

III. Active/Passive Immunization and Treatment/Prevention of Chikungunya Infection

A. Formulation and Administration

The present disclosure provides pharmaceutical compositions comprising anti-Chikungunya virus antibodies and antigens for generating the same. Such compositions

comprise a prophylactically or therapeutically effective amount of an antibody or a fragment thereof, or a peptide immunogen, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a particular carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Other suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like.

The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, *etc.* Examples of suitable pharmaceutical agents are described in "Remington's Pharmaceutical Sciences." Such compositions will contain a prophylactically or therapeutically effective amount of the antibody or fragment thereof, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration, which can be oral, intravenous, intraarterial, intrabuccal, intranasal, nebulized, bronchial inhalation, or delivered by mechanical ventilation.

Active vaccines are also envisioned where antibodies like those that are disclosed are produced *in vivo* in a subject at risk of Chikungunya virus infection. Sequences for the E1 and E2 are listed as SEQ ID NOS: 253-276 in the appended sequence listing. Such vaccines can be formulated for parenteral administration, *e.g.*, formulated for injection *via* the intradermal, intravenous, intramuscular, subcutaneous, or even intraperitoneal routes. Administration by intradermal and intramuscular routes are contemplated. The vaccine could alternatively be administered by a topical route directly to the mucosa, for example by nasal drops, inhalation, or by nebulizer. Pharmaceutically acceptable salts, include the acid salts

and those which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups may also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

Passive transfer of antibodies, known as artificially acquired passive immunity, generally will involve the use of intravenous or intramuscular injections. The forms of antibody can be human or animal blood plasma or serum, as pooled human immunoglobulin for intravenous (IVIG) or intramuscular (IG) use, as high-titer human IVIG or IG from immunized or from donors recovering from disease, and as monoclonal antibodies (MAb). Such immunity generally lasts for only a short period of time, and there is also a potential risk for hypersensitivity reactions, and serum sickness, especially from gamma globulin of non-human origin. However, passive immunity provides immediate protection. The antibodies will be formulated in a carrier suitable for injection, *i.e.*, sterile and syringeable.

Generally, the ingredients of compositions of the disclosure are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water-free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compositions of the disclosure can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, *etc.*, and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, *etc.*

IV. Antibody Conjugates

Antibodies of the present disclosure may be linked to at least one agent to form an antibody conjugate. In order to increase the efficacy of antibody molecules as diagnostic or therapeutic agents, it is conventional to link or covalently bind or complex at least one desired molecule or moiety. Such a molecule or moiety may be, but is not limited to, at least

one effector or reporter molecule. Effector molecules comprise molecules having a desired activity, *e.g.*, cytotoxic activity. Non-limiting examples of effector molecules which have been attached to antibodies include toxins, anti-tumor agents, therapeutic enzymes, radionuclides, antiviral agents, chelating agents, cytokines, growth factors, and oligo- or polynucleotides. By contrast, a reporter molecule is defined as any moiety which may be detected using an assay. Non-limiting examples of reporter molecules which have been conjugated to antibodies include enzymes, radiolabels, haptens, fluorescent labels, phosphorescent molecules, chemiluminescent molecules, chromophores, photoaffinity molecules, colored particles or ligands, such as biotin.

Antibody conjugates are generally preferred for use as diagnostic agents. Antibody diagnostics generally fall within two classes, those for use in *in vitro* diagnostics, such as in a variety of immunoassays, and those for use *in vivo* diagnostic protocols, generally known as "antibody-directed imaging." Many appropriate imaging agents are known in the art, as are methods for their attachment to antibodies (see, for *e.g.*, U.S. Patents 5,021,236, 4,938,948, and 4,472,509). The imaging moieties used can be paramagnetic ions, radioactive isotopes, fluorochromes, NMR-detectable substances, and X-ray imaging agents.

In the case of paramagnetic ions, one might mention by way of example ions such as chromium (III), manganese (II), iron (III), iron (II), cobalt (II), nickel (II), copper (II), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), vanadium (II), terbium (III), dysprosium (III), holmium (III) and/or erbium (III), with gadolinium being particularly preferred. Ions useful in other contexts, such as X-ray imaging, include but are not limited to lanthanum (III), gold (III), lead (II), and especially bismuth (III).

In the case of radioactive isotopes for therapeutic and/or diagnostic application, one might mention astatine^{211}, ^{14}carbon, ^{51}chromium, ^{36}chlorine, ^{57}cobalt, ^{58}cobalt, copper^{67}, ^{152}Eu, gallium^{67}, ^{3}hydrogen, iodine^{123}, iodine^{125}, iodine^{131}, indium^{111}, ^{59}iron, ^{32}phosphorus, rhenium^{186}, rhenium^{188}, ^{75}selenium, ^{35}sulphur, technicium^{99m} and/or yttrium^{90}. ^{125}I is often being preferred for use in certain embodiments, and technicium^{99m} and/or indium^{111} are also often preferred due to their low energy and suitability for long range detection. Radioactively labeled monoclonal antibodies of the present disclosure may be produced according to well-known methods in the art. For instance, monoclonal antibodies can be iodinated by contact with sodium and/or potassium iodide and a chemical oxidizing agent such as sodium hypochlorite, or an enzymatic oxidizing agent, such as lactoperoxidase. Monoclonal antibodies according to the disclosure may be labeled with technetium^{99m} by ligand exchange process, for example, by reducing pertechnate with stannous solution, chelating the reduced

technetium onto a Sephadex column and applying the antibody to this column. Alternatively, direct labeling techniques may be used, *e.g.*, by incubating pertechnate, a reducing agent such as $SNCl_2$, a buffer solution such as sodium-potassium phthalate solution, and the antibody. Intermediary functional groups which are often used to bind radioisotopes which exist as metallic ions to antibody are diethylenetriaminepentaacetic acid (DTPA) or ethylene diaminetetracetic acid (EDTA).

Among the fluorescent labels contemplated for use as conjugates include Alexa 350, Alexa 430, AMCA, BODIPY 630/650, BODIPY 650/665, BODIPY-FL, BODIPY-R6G, BODIPY-TMR, BODIPY-TRX, Cascade Blue, Cy3, Cy5,6-FAM, Fluorescein Isothiocyanate, HEX, 6-JOE, Oregon Green 488, Oregon Green 500, Oregon Green 514, Pacific Blue, REG, Rhodamine Green, Rhodamine Red, Renographin, ROX, TAMRA, TET, Tetramethylrhodamine, and/or Texas Red.

Another type of antibody conjugates contemplated in the present disclosure are those intended primarily for use *in vitro*, where the antibody is linked to a secondary binding ligand and/or to an enzyme (an enzyme tag) that will generate a colored product upon contact with a chromogenic substrate. Examples of suitable enzymes include urease, alkaline phosphatase, (horseradish) hydrogen peroxidase or glucose oxidase. Preferred secondary binding ligands are biotin and avidin and streptavidin compounds. The use of such labels is well known to those of skill in the art and are described, for example, in U.S. Patents 3,817,837, 3,850,752, 3,939,350, 3,996,345, 4,277,437, 4,275,149 and 4,366,241.

Yet another known method of site-specific attachment of molecules to antibodies comprises the reaction of antibodies with hapten-based affinity labels. Essentially, hapten-based affinity labels react with amino acids in the antigen binding site, thereby destroying this site and blocking specific antigen reaction. However, this may not be advantageous since it results in loss of antigen binding by the antibody conjugate.

Molecules containing azido groups may also be used to form covalent bonds to proteins through reactive nitrene intermediates that are generated by low intensity ultraviolet light (Potter and Haley, 1983). In particular, 2- and 8-azido analogues of purine nucleotides have been used as site-directed photoprobes to identify nucleotide binding proteins in crude cell extracts (Owens & Haley, 1987; Atherton *et al.*, 1985). The 2- and 8-azido nucleotides have also been used to map nucleotide binding domains of purified proteins (Khatoon *et al.*, 1989; King *et al.*, 1989; Dholakia *et al.*, 1989) and may be used as antibody binding agents.

Several methods are known in the art for the attachment or conjugation of an antibody to its conjugate moiety. Some attachment methods involve the use of a metal chelate complex

employing, for example, an organic chelating agent such a diethylenetriaminepentaacetic acid anhydride (DTPA); ethylenetriaminetetraacetic acid; N-chloro-p-toluenesulfonamide; and/or tetrachloro-3α-6α-diphenylglycouril-3 attached to the antibody (U.S. Patents 4,472,509 and 4,938,948). Monoclonal antibodies may also be reacted with an enzyme in the presence of a coupling agent such as glutaraldehyde or periodate. Conjugates with fluorescein markers are prepared in the presence of these coupling agents or by reaction with an isothiocyanate. In U.S. Patent 4,938,948, imaging of breast tumors is achieved using monoclonal antibodies and the detectable imaging moieties are bound to the antibody using linkers such as methyl-p-hydroxybenzimidate or N-succinimidyl-3-(4-hydroxyphenyl)propionate.

In other embodiments, derivatization of immunoglobulins by selectively introducing sulfhydryl groups in the Fc region of an immunoglobulin, using reaction conditions that do not alter the antibody combining site are contemplated. Antibody conjugates produced according to this methodology are disclosed to exhibit improved longevity, specificity and sensitivity (U.S. Patent 5,196,066, incorporated herein by reference). Site-specific attachment of effector or reporter molecules, wherein the reporter or effector molecule is conjugated to a carbohydrate residue in the Fc region have also been disclosed in the literature (O'Shannessy *et al.*, 1987). This approach has been reported to produce diagnostically and therapeutically promising antibodies which are currently in clinical evaluation.

V. Immunodetection Methods

In still further embodiments, the present disclosure concerns immunodetection methods for binding, purifying, removing, quantifying and otherwise generally detecting Chikungunya virus and its associated antigens. While such methods can be applied in a traditional sense, another use will be in quality control and monitoring of vaccine and other virus stocks, where antibodies according to the present disclosure can be used to assess the amount or integrity (*i.e.*, long term stability) of H1 antigens in viruses. Alternatively, the methods may be used to screen various antibodies for appropriate/desired reactivity profiles.

Some immunodetection methods include enzyme linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunoradiometric assay, fluoroimmunoassay, chemiluminescent assay, bioluminescent assay, and Western blot to mention a few. In particular, a competitive assay for the detection and quantitation of Chikungunya virus antibodies directed to specific parasite epitopes in samples also is provided. The steps of various useful immunodetection methods have been described in the scientific literature, such

as, *e.g.*, Doolittle and Ben-Zeev (1999), Gulbis and Galand (1993), De Jager *et al.* (1993), and Nakamura *et al.* (1987). In general, the immunobinding methods include obtaining a sample suspected of containing Chikungunya virus, and contacting the sample with a first antibody in accordance with the present disclosure, as the case may be, under conditions effective to allow the formation of immunocomplexes.

These methods include methods for purifying Chikungunya virus or related antigens from a sample. The antibody will preferably be linked to a solid support, such as in the form of a column matrix, and the sample suspected of containing the Chikungunya virus or antigenic component will be applied to the immobilized antibody. The unwanted components will be washed from the column, leaving the Chikungunya virus antigen immunocomplexed to the immobilized antibody, which is then collected by removing the organism or antigen from the column.

The immunobinding methods also include methods for detecting and quantifying the amount of Chikungunya virus or related components in a sample and the detection and quantification of any immune complexes formed during the binding process. Here, one would obtain a sample suspected of containing Chikungunya virus or its antigens, and contact the sample with an antibody that binds Chikungunya virus or components thereof, followed by detecting and quantifying the amount of immune complexes formed under the specific conditions. In terms of antigen detection, the biological sample analyzed may be any sample that is suspected of containing Chikungunya virus or Chikungunya virus antigen, such as a tissue section or specimen, a homogenized tissue extract, a biological fluid, including blood and serum, or a secretion, such as feces or urine.

Contacting the chosen biological sample with the antibody under effective conditions and for a period of time sufficient to allow the formation of immune complexes (primary immune complexes) is generally a matter of simply adding the antibody composition to the sample and incubating the mixture for a period of time long enough for the antibodies to form immune complexes with, *i.e.*, to bind to Chikungunya virus or antigens present. After this time, the sample-antibody composition, such as a tissue section, ELISA plate, dot blot or Western blot, will generally be washed to remove any non-specifically bound antibody species, allowing only those antibodies specifically bound within the primary immune complexes to be detected.

In general, the detection of immunocomplex formation is well known in the art and may be achieved through the application of numerous approaches. These methods are generally based upon the detection of a label or marker, such as any of those radioactive,

fluorescent, biological and enzymatic tags. Patents concerning the use of such labels include U.S. Patents 3,817,837, 3,850,752, 3,939,350, 3,996,345, 4,277,437, 4,275,149 and 4,366,241. Of course, one may find additional advantages through the use of a secondary binding ligand such as a second antibody and/or a biotin/avidin ligand binding arrangement, as is known in the art.

The antibody employed in the detection may itself be linked to a detectable label, wherein one would then simply detect this label, thereby allowing the amount of the primary immune complexes in the composition to be determined. Alternatively, the first antibody that becomes bound within the primary immune complexes may be detected by means of a second binding ligand that has binding affinity for the antibody. In these cases, the second binding ligand may be linked to a detectable label. The second binding ligand is itself often an antibody, which may thus be termed a "secondary" antibody. The primary immune complexes are contacted with the labeled, secondary binding ligand, or antibody, under effective conditions and for a period of time sufficient to allow the formation of secondary immune complexes. The secondary immune complexes are then generally washed to remove any non-specifically bound labeled secondary antibodies or ligands, and the remaining label in the secondary immune complexes is then detected.

Further methods include the detection of primary immune complexes by a two-step approach. A second binding ligand, such as an antibody that has binding affinity for the antibody, is used to form secondary immune complexes, as described above. After washing, the secondary immune complexes are contacted with a third binding ligand or antibody that has binding affinity for the second antibody, again under effective conditions and for a period of time sufficient to allow the formation of immune complexes (tertiary immune complexes). The third ligand or antibody is linked to a detectable label, allowing detection of the tertiary immune complexes thus formed. This system may provide for signal amplification if this is desired.

One method of immunodetection uses two different antibodies. A first biotinylated antibody is used to detect the target antigen, and a second antibody is then used to detect the biotin attached to the complexed biotin. In that method, the sample to be tested is first incubated in a solution containing the first step antibody. If the target antigen is present, some of the antibody binds to the antigen to form a biotinylated antibody/antigen complex. The antibody/antigen complex is then amplified by incubation in successive solutions of streptavidin (or avidin), biotinylated DNA, and/or complementary biotinylated DNA, with each step adding additional biotin sites to the antibody/antigen complex. The amplification

steps are repeated until a suitable level of amplification is achieved, at which point the sample is incubated in a solution containing the second step antibody against biotin. This second step antibody is labeled, as for example with an enzyme that can be used to detect the presence of the antibody/antigen complex by histoenzymology using a chromogen substrate. With suitable amplification, a conjugate can be produced which is macroscopically visible.

Another known method of immunodetection takes advantage of the immuno-PCR (Polymerase Chain Reaction) methodology. The PCR method is similar to the Cantor method up to the incubation with biotinylated DNA, however, instead of using multiple rounds of streptavidin and biotinylated DNA incubation, the DNA/biotin/streptavidin/antibody complex is washed out with a low pH or high salt buffer that releases the antibody. The resulting wash solution is then used to carry out a PCR reaction with suitable primers with appropriate controls. At least in theory, the enormous amplification capability and specificity of PCR can be utilized to detect a single antigen molecule.

A. ELISAs

Immunoassays, in their most simple and direct sense, are binding assays. Certain preferred immunoassays are the various types of enzyme linked immunosorbent assays (ELISAs) and radioimmunoassays (RIA) known in the art. Immunohistochemical detection using tissue sections is also particularly useful. However, it will be readily appreciated that detection is not limited to such techniques, and western blotting, dot blotting, FACS analyses, and the like may also be used.

In one exemplary ELISA, the antibodies of the disclosure are immobilized onto a selected surface exhibiting protein affinity, such as a well in a polystyrene microtiter plate. Then, a test composition suspected of containing the Chikungunya virus or Chikungunya virus antigen is added to the wells. After binding and washing to remove non-specifically bound immune complexes, the bound antigen may be detected. Detection may be achieved by the addition of another anti-Chikungunya virus antibody that is linked to a detectable label. This type of ELISA is a simple "sandwich ELISA." Detection may also be achieved by the addition of a second anti-Chikungunya virus antibody, followed by the addition of a third antibody that has binding affinity for the second antibody, with the third antibody being linked to a detectable label.

In another exemplary ELISA, the samples suspected of containing the Chikungunya virus or Chikungunya virus antigen are immobilized onto the well surface and then contacted with the anti- Chikungunya virus antibodies of the disclosure. After binding and washing to

remove non-specifically bound immune complexes, the bound anti-Chikungunya virus antibodies are detected. Where the initial anti-Chikungunya virus antibodies are linked to a detectable label, the immune complexes may be detected directly. Again, the immune complexes may be detected using a second antibody that has binding affinity for the first anti-Chikungunya virus antibody, with the second antibody being linked to a detectable label.

Irrespective of the format employed, ELISAs have certain features in common, such as coating, incubating and binding, washing to remove non-specifically bound species, and detecting the bound immune complexes. These are described below.

In coating a plate with either antigen or antibody, one will generally incubate the wells of the plate with a solution of the antigen or antibody, either overnight or for a specified period of hours. The wells of the plate will then be washed to remove incompletely adsorbed material. Any remaining available surfaces of the wells are then "coated" with a nonspecific protein that is antigenically neutral with regard to the test antisera. These include bovine serum albumin (BSA), casein or solutions of milk powder. The coating allows for blocking of nonspecific adsorption sites on the immobilizing surface and thus reduces the background caused by nonspecific binding of antisera onto the surface.

In ELISAs, it is probably more customary to use a secondary or tertiary detection means rather than a direct procedure. Thus, after binding of a protein or antibody to the well, coating with a non-reactive material to reduce background, and washing to remove unbound material, the immobilizing surface is contacted with the biological sample to be tested under conditions effective to allow immune complex (antigen/antibody) formation. Detection of the immune complex then requires a labeled secondary binding ligand or antibody, and a secondary binding ligand or antibody in conjunction with a labeled tertiary antibody or a third binding ligand.

"Under conditions effective to allow immune complex (antigen/antibody) formation" means that the conditions preferably include diluting the antigens and/or antibodies with solutions such as BSA, bovine gamma globulin (BGG) or phosphate buffered saline (PBS)/Tween. These added agents also tend to assist in the reduction of nonspecific background.

The "suitable" conditions also mean that the incubation is at a temperature or for a period of time sufficient to allow effective binding. Incubation steps are typically from about 1 to 2 to 4 hours or so, at temperatures preferably on the order of 25°C to 27°C, or may be overnight at about 4°C or so.

Following all incubation steps in an ELISA, the contacted surface is washed so as to remove non-complexed material. A preferred washing procedure includes washing with a solution such as PBS/Tween, or borate buffer. Following the formation of specific immune complexes between the test sample and the originally bound material, and subsequent washing, the occurrence of even minute amounts of immune complexes may be determined.

To provide a detecting means, the second or third antibody will have an associated label to allow detection. Preferably, this will be an enzyme that will generate color development upon incubating with an appropriate chromogenic substrate. Thus, for example, one will desire to contact or incubate the first and second immune complex with a urease, glucose oxidase, alkaline phosphatase or hydrogen peroxidase-conjugated antibody for a period of time and under conditions that favor the development of further immune complex formation (*e.g.*, incubation for 2 hours at room temperature in a PBS-containing solution such as PBS-Tween).

After incubation with the labeled antibody, and subsequent to washing to remove unbound material, the amount of label is quantified, *e.g.*, by incubation with a chromogenic substrate such as urea, or bromocresol purple, or 2,2'-azino-di-(3-ethyl-benzthiazoline-6-sulfonic acid (ABTS), or H_2O_2, in the case of peroxidase as the enzyme label. Quantification is then achieved by measuring the degree of color generated, *e.g.*, using a visible spectra spectrophotometer.

In another embodiment, the present disclosure contemplates the use of competitive formats. This is particularly useful in the detection of Chikungunya virus antibodies in sample. In competition based assays, an unknown amount of analyte or antibody is determined by its ability to displace a known amount of labeled antibody or analyte. Thus, the quantifiable loss of a signal is an indication of the amount of unknown antibody or analyte in a sample.

Here, the inventors propose the use of labeled Chikungunya virus monoclonal antibodies to determine the amount of Chikungunya virus antibodies in a sample. The basic format would include contacting a known amount of Chikungunya virus monoclonal antibody (linked to a detectable label) with Chikungunya virus antigen or particle. The Chikungunya virus antigen or organism is preferably attached to a support. After binding of the labeled monoclonal antibody to the support, the sample is added and incubated under conditions permitting any unlabeled antibody in the sample to compete with, and hence displace, the labeled monoclonal antibody. By measuring either the lost label or the label remaining (and subtracting that from the original amount of bound label), one can determine

how much non-labeled antibody is bound to the support, and thus how much antibody was present in the sample.

B. Western Blot

The Western blot (alternatively, protein immunoblot) is an analytical technique used to detect specific proteins in a given sample of tissue homogenate or extract. It uses gel electrophoresis to separate native or denatured proteins by the length of the polypeptide (denaturing conditions) or by the 3-D structure of the protein (native/ non-denaturing conditions). The proteins are then transferred to a membrane (typically nitrocellulose or PVDF), where they are probed (detected) using antibodies specific to the target protein.

Samples may be taken from whole tissue or from cell culture. In most cases, solid tissues are first broken down mechanically using a blender (for larger sample volumes), using a homogenizer (smaller volumes), or by sonication. Cells may also be broken open by one of the above mechanical methods. However, it should be noted that bacteria, virus or environmental samples can be the source of protein and thus Western blotting is not restricted to cellular studies only. Assorted detergents, salts, and buffers may be employed to encourage lysis of cells and to solubilize proteins. Protease and phosphatase inhibitors are often added to prevent the digestion of the sample by its own enzymes. Tissue preparation is often done at cold temperatures to avoid protein denaturing.

The proteins of the sample are separated using gel electrophoresis. Separation of proteins may be by isoelectric point (pI), molecular weight, electric charge, or a combination of these factors. The nature of the separation depends on the treatment of the sample and the nature of the gel. This is a very useful way to determine a protein. It is also possible to use a two-dimensional (2-D) gel which spreads the proteins from a single sample out in two dimensions. Proteins are separated according to isoelectric point (pH at which they have neutral net charge) in the first dimension, and according to their molecular weight in the second dimension.

In order to make the proteins accessible to antibody detection, they are moved from within the gel onto a membrane made of nitrocellulose or polyvinylidene difluoride (PVDF). The membrane is placed on top of the gel, and a stack of filter papers placed on top of that. The entire stack is placed in a buffer solution which moves up the paper by capillary action, bringing the proteins with it. Another method for transferring the proteins is called electroblotting and uses an electric current to pull proteins from the gel into the PVDF or nitrocellulose membrane. The proteins move from within the gel onto the membrane while

maintaining the organization they had within the gel. As a result of this blotting process, the proteins are exposed on a thin surface layer for detection (see below). Both varieties of membrane are chosen for their non-specific protein binding properties (*i.e.*, binds all proteins equally well). Protein binding is based upon hydrophobic interactions, as well as charged interactions between the membrane and protein. Nitrocellulose membranes are cheaper than PVDF, but are far more fragile and do not stand up well to repeated probings. The uniformity and overall effectiveness of transfer of protein from the gel to the membrane can be checked by staining the membrane with Coomassie Brilliant Blue or Ponceau S dyes. Once transferred, proteins are detected using labeled primary antibodies, or unlabeled primary antibodies followed by indirect detection using labeled protein A or secondary labeled antibodies binding to the Fc region of the primary antibodies.

C. Immunohistochemistry

The antibodies of the present disclosure may also be used in conjunction with both fresh-frozen and/or formalin-fixed, paraffin-embedded tissue blocks prepared for study by immunohistochemistry (IHC). The method of preparing tissue blocks from these particulate specimens has been successfully used in previous IHC studies of various prognostic factors, and is well known to those of skill in the art (Brown *et al.*, 1990; Abbondanzo *et al.*, 1990; Allred *et al.*, 1990).

Briefly, frozen-sections may be prepared by rehydrating 50 ng of frozen "pulverized" tissue at room temperature in phosphate buffered saline (PBS) in small plastic capsules; pelleting the particles by centrifugation; resuspending them in a viscous embedding medium (OCT); inverting the capsule and/or pelleting again by centrifugation; snap-freezing in -70°C isopentane; cutting the plastic capsule and/or removing the frozen cylinder of tissue; securing the tissue cylinder on a cryostat microtome chuck; and/or cutting 25-50 serial sections from the capsule. Alternatively, whole frozen tissue samples may be used for serial section cuttings.

Permanent-sections may be prepared by a similar method involving rehydration of the 50 mg sample in a plastic microfuge tube; pelleting; resuspending in 10% formalin for 4 hours fixation; washing/pelleting; resuspending in warm 2.5% agar; pelleting; cooling in ice water to harden the agar; removing the tissue/agar block from the tube; infiltrating and/or embedding the block in paraffin; and/or cutting up to 50 serial permanent sections. Again, whole tissue samples may be substituted.

D. Immunodetection Kits

In still further embodiments, the present disclosure concerns immunodetection kits for use with the immunodetection methods described above. As the antibodies may be used to detect Chikungunya virus or Chikungunya virus antigens, the antibodies may be included in the kit. The immunodetection kits will thus comprise, in suitable container means, a first antibody that binds to Chikungunya virus or Chikungunya virus antigen, and optionally an immunodetection reagent.

In certain embodiments, the Chikungunya virus antibody may be pre-bound to a solid support, such as a column matrix and/or well of a microtitre plate. The immunodetection reagents of the kit may take any one of a variety of forms, including those detectable labels that are associated with or linked to the given antibody. Detectable labels that are associated with or attached to a secondary binding ligand are also contemplated. Exemplary secondary ligands are those secondary antibodies that have binding affinity for the first antibody.

Further suitable immunodetection reagents for use in the present kits include the two-component reagent that comprises a secondary antibody that has binding affinity for the first antibody, along with a third antibody that has binding affinity for the second antibody, the third antibody being linked to a detectable label. As noted above, a number of exemplary labels are known in the art and all such labels may be employed in connection with the present disclosure.

The kits may further comprise a suitably aliquoted composition of the Chikungunya virus or Chikungunya virus antigens, whether labeled or unlabeled, as may be used to prepare a standard curve for a detection assay. The kits may contain antibody-label conjugates either in fully conjugated form, in the form of intermediates, or as separate moieties to be conjugated by the user of the kit. The components of the kits may be packaged either in aqueous media or in lyophilized form.

The container means of the kits will generally include at least one vial, test tube, flask, bottle, syringe or other container means, into which the antibody may be placed, or preferably, suitably aliquoted. The kits of the present disclosure will also typically include a means for containing the antibody, antigen, and any other reagent containers in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which the desired vials are retained.

VI. Examples

The following examples are included to demonstrate preferred embodiments. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent techniques discovered by the inventors to function well in the practice of embodiments, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

Example 1 - Materials and Methods

Isolation of human mAbs. PBMCs were obtained from a human ~ 5 years after documented symptomatic CHKV infection in Sri Lanka. B cells were transformed in 384-well plates with EBV in the presence of CpG. The supernatants from the resulting B cell lymphoblastic cells lines were screened for the presence of human CHKV-specific binding antibodies by ELISA using live CHIKV vaccine strain 181/25 virus as antigen. Transformed B cells were collected and fused to a myeloma cell line, distributed into culture plates and expansion, and selected by growth in hypoxanthine-aminopterin-thymidine medium containing ouabain. Hybridomas were cloned by single-cell sorting. Supernatants from cloned hybridomas growing in serum-free medium were collected, purified and concentrated from clarified medium by protein G chromatography.

Neutralization assays. Purified IgG mAb proteins were tested for neutralizing activity using CHKV virus replicon particles (VRPs) or each of 4 live chikungunya viruses representing diverse genetic and geographic profile. A CHIKV VRP that encoded GFP was generated by development of a three-plasmid CHIKV replicon helper system based on a plasmid containing the full-length cDNA of the CHIKV strain SL15649 (GenBank: GU189061.1) genome sequence, using PCR-based cloning methodologies. VRP were incubated with mAb in dilutions then inoculated onto Vero 81 cell monolayers for 18 hrs; infected cells and total cells (identified with a nuclear marker) were identified with a fluorescence imaging system. To determine mAb breadth and neutralization potency, the inventors used four representative live virus strains with at least one representative from each CHIKV genotype, including one prototype virus from each of the three genotypes and also a strain from the current Caribbean outbreak. Neutralizing activity was determined in a focus reduction neutralization test. Serial dilutions of purified human mAbs were incubated with

100 focus-forming units of CHIKV at 37°C for 1 hour. MAb-virus complexes were added to Vero cells in 96-well plates, and then plaques were detected after cell fixation using immunoperoxidase detection and quantified using an ImmunoSpot 5.0.37 macroanalyzer (Cellular Technologies Ltd). EC_{50} values were calculated using nonlinear regression analysis after comparison to wells inoculated with CHIKV in the absence of antibody.

E2 ELISA. Recombinant CHIKV E2 ectodomain protein (corresponding to the CHIKV-LR2006 strain) was generated in *E. coli* and adsorbed to microtiter plates. Human mAbs were applied, then bound CHKV-specific mAbs were detected with biotin-conjugated goat anti-human IgG.

Competition binding assay. The inventors identified groups of antibodies binding to the same major antigenic site by competing pairs of antibodies for binding to CHIKV-LR2006 E2 ectodomain protein containing a polyhistidine-tag attached to an Anti-Penta-His biosensor tip (ForteBio #18-5077) in an Octet Red biosensor (ForteBio).

Alanine scanning mutagenesis for epitope mapping. A CHIKV envelope protein expression construct (strain S27, Uniprot Reference #Q8JUX5) with a C-terminal V5 tag was subjected to alanine-scanning mutagenesis to generate a comprehensive mutation library. Primers were designed to mutate each residue within the E2, 6K, and E1 regions of the envelope proteins (residues Y326 to H1248 in the structural polyprotein) to alanine; alanine codons were mutated to serine. In total, 910 CHIKV envelope protein mutants were generated. Loss of binding of mAbs to each construct was tested using an immunofluorescence binding assay, using cellular fluorescence detected with a high-throughput flow cytometer.

Mechanism of neutralization. MAbs were interacted with VRPs before or after attachment to Vero 81 cells, and then cells were stained, imaged, and analyzed as described for VRP neutralization assays to determine at what stage mAbs exerted the antiviral effect. Fusion from within and fusion from without assays were performed as detailed in Supplemental Experimental Procedures.

***In vivo* protection studies in mice.** *Ifnar*$^{-/-}$ mice were bred in pathogen-free animal facilities and infection experiments were performed in A-BSL3 facilities. Footpad injections were performed under anesthesia. For prophylaxis studies, human mAbs were administered by intraperitoneal injection to 6 week-old *Ifnar*$^{-/-}$ mice 1 day prior to subcutaneous inoculation in the footpad with 10 FFU of CHIKV-LR. For therapeutic studies, 10 FFU of CHIKV-LR was delivered 24, 48, or 60 hours prior to administration of a single dose of individual or combinations of human mAbs at specified doses.

Human subject and peripheral blood cell isolation. An otherwise healthy adult subject presented in October of 2006 with CHIKV infection. The symptoms of CHIKV infection coincided with return from a one-year visit to Sri Lanka, during which the patient spent time in urban areas (primarily Colombo), and rural settings, including rainforests and coastal areas. The patient experienced multiple insect bites over the course of the visit, but remained in good health throughout the stay. On return to the U.S., the subject presented to the primary care physician with a fever (102°F) of three days duration. The patient reported the concurrent development of bilateral joint pain in elbows and fingers, and a raised, non-pruritic rash on the back and abdomen, accompanied by general "body ache" and headache. On presentation, he appeared to be well, and in no acute distress. A mild, blanching, papular rash extended across the back, chest and abdomen (see FIG. 4). A mild conjunctivitis was noted. The skeletal exam was remarkable for tender swollen fingers, knees and elbows, which were without erythema or effusions. Muscle strength and range of motion of the affected joints were intact, but joint movement elicited pain.

Blood was drawn for a CBC, serologies and malaria smears, and the patient was discharged. The white blood cell count was 4.0×10^4 cells/mm^3, the hematocrit was 41% and platelet count was 180,000/mm^3. The total lymphocyte count was 1.0×10^4 cells/mm^3. Malaria smears and serologies were negative, and the patient was diagnosed tentatively as having a viral illness of unknown etiology.

The patient returned to the clinic two weeks later, afebrile, but with persistent arthralgia, most prominent in the fingers. The patient described the pain and stiffness as no better, and perhaps worse, than during his previous visit. The patient reported that an outbreak of chikungunya was occurring in the area of previous travel. Blood was drawn and serum separated and sent to CDC for PCR and serological testing, which confirmed the diagnosis of chikungunya infection.

In April 2012, five and a half years after the index infection, peripheral blood mononuclear cells (PBMCs) were isolated by density gradient separation on Ficoll without known exposure to CHIKV or other arthritogenic alphaviruses in the intervening period while living in the United States. The cells were cryopreserved and stored in liquid nitrogen until study. The protocol for recruiting and collecting blood samples from subjects was approved by the Institutional Review Boards of the University of North Carolina at Chapel Hill and the Vanderbilt University Medical Center.

Generation of human hybridomas. Cryopreserved PBMC samples were thawed rapidly at 37°C and washed prior to transformation with Epstein-Barr virus, as described (Smith *et al.*, 2012). Cultures were incubated at 37°C with 5% CO_2 for 10 days and screened for the presence of cells secreting CHIKV-specific antibodies in the supernatant using VRP neutralizing assays and an ELISA. The inventors performed two independent transformations using separate aliquots of the same blood sample.

In the first transformation, the inventors established 3,840 cultures (10 x 384-well plates) containing an average of 42 transformed B cell colonies per culture, for an estimated total of about 161,000 individual B cell colonies. To screen for antibodies that display neutralizing activity against CHIKV under BSL2 conditions, the inventors developed a high-throughput fluorescence reduction neutralization assay using CHIKV replicon particles (VRPs) that express green fluorescent protein as a reporter. VRPs are virions that display the native viral glycoproteins but lack the full-length viral genome and thus are incapable of generating infectious progeny (Vander Veen *et al.*, 2012). The inventors used VRPs derived from strain SL15649 (Morrison *et al.*, 2011), which was isolated from Sri Lanka in 2006. SL15649 is contemporaneous to the strain that infected the donor and is likely very similar in sequence. From this experiment, the inventors identified 160 B cell cultures with supernatants that mediated neutralization at 90% inhibition, suggesting a frequency of 0.099% virus-specific B cells per total B cells (~ 1 in 1,000). A total of 60 of these lines inhibited at a level of > 98%, and in the secondary screen, supernatants from 58 of the 60 lines contained antibodies that bound in ELISA to cell-culture-produced CHIKV (strain 181/25) captured on an immunoassay plate. The inventors selected 35 of the 58 lines with the highest neutralizing and binding activity for hybridoma fusion, identified 22 hybridomas with virus-binding supernatants after fusion and plating, and successfully isolated 14 clones for further study. In the second transformation, the inventors established 1,536 cultures (4 x 384-well plates) containing an average of 38 transformed B cell colonies per culture, for an estimated total of about 58,000 individual B cell colonies tested, suggesting a virus-specific B cell frequency of 0.1% (again, ~ 1 in 1,000). In this experiment, they used a primary screen of ELISA binding to CHIKV strain 181/25 without a prior neutralizing test. The inventors identified 60 lines with ELISA optical density signal greater than four times the background level, selected the 30 B cell lines with the highest optical density signal in ELISA for fusion, identified 18 hybridomas with virus-binding supernatants after fusion and plating, and successfully isolated 16 clones for further study.

Fusion with myeloma cells. Cells from wells with supernatants capable of neutralizing CHIKV infectivity were fused with HMMA2.5 non-secreting myeloma cells as described (Smith *et al.*, 2012). Resultant hybridomas were selected by growth in hypoxanthine-aminopterin-thymidine (HAT) medium containing ouabain, biologically cloned by single-cell FACS using a FACSAria III cell sorter (BD Biosciences), and expanded.

Human mAb production and purification. Wells containing hybridomas producing CHIKV-specific antibodies were cloned by three rounds of limiting dilution or with a ClonePix device (Molecular Devices) according to the manufacturer's instructions. Once individual clones were obtained, each hybridoma was expanded until 50% confluent in 75 cm^2 flasks. For antibody expression, cells were collected with a cell scraper, washed in serum-free medium (GIBCO Hybridoma-SFM from Invitrogen, 12045084), and divided equally into four 225 cm^2 flasks (Corning, 431082) containing 250 mL serum-free medium. Cells were incubated for 21 days before medium was clarified by centrifugation and passed through a 0.2 μm sterile filter. Antibodies were purified from clarified medium by protein G chromatography (GE Life Sciences, Protein G HP Columns).

Cells. BHK-21 cells (ATCC CCL-10) were maintained in alpha minimal essential medium (αMEM; Gibco) supplemented to contain 10% fetal bovine serum (FBS) and 10% tryptose phosphate (Sigma). Vero 81 cells (ATCC CCL-81) were maintained in αMEM supplemented to contain 5% FBS. Medium for all cells was supplemented to contain 0.29 mg/mL L-glutamine (Gibco), 100 U/mL penicillin (Gibco), 100 μg/mL streptomycin (Gibco), and 500 ng/mL amphotericin B. Cells were maintained at 37°C in a humidified atmosphere of 5% CO_2.

Generation of CHIKV VRP plasmid constructs. A three-plasmid CHIKV replicon helper system was derived from a plasmid containing the full-length cDNA of the CHIKV strain SL15649 (GenBank: GU189061.1) genome sequence using PCR-based cloning methodologies. A CHIKV replicon genome was constructed using a two-step process that involved the generation of an intermediate cloning vector with the CHIKV full-length structural cassette substituted with a multiple cloning site (MCS). Enhanced green fluorescent protein (eGFP) was subcloned into the multiple cloning site of this plasmid to generate pMH41 (CHIKV SL15649 eGFP replicon). The construction of a two-plasmid helper system included a multi-step cloning process that first involved the generation of a full-length structural gene helper plasmid via removal of the majority (6,891 nt) of the CHIKV non-structural cassette. The full-length structural cassette was further subdivided into two

constructs, pMH38 (CHIKV SL15649 capsid helper), which is comprised of the capsid gene sequence followed by a unique AvrII restriction site, and pMH39 (CHIKV SL15649 glycoprotein helper), which contains an in-frame deletion of the capsid RNA-binding domain followed by the intact envelope glycoprotein (E3-E1) coding sequence.

Recombinant CHIKV p62-E1 production. A plasmid containing CHIKV p62 (*i.e.*, E3 [aa S1-R64] - E2 [aa S1–E361] -16 amino acid linker - E1 [aa Y1-Q411] followed by a His tag) (Voss *et al.*, 2010) was transfected into 293F cells using 293fectin reagent (Invitrogen). After 72 hours incubation, the supernatant was removed, and the cells were cultured for an additional 72 hours. The pooled supernatants were loaded onto a nickel agarose bead column (GoldBio) and eluted with imidazole. The protein was further purified using a Superdex S200 gel filtration column (GE Life Sciences). Fractions containing the CHIKV p62-E1 protein were pooled, frozen, and stored at -80°C.

Generation of CHIKV strain SL15649-derived VRP stocks. VRP stocks were recovered from recombinant CHIKV plasmids in a certified biological safety level 3 (BSL3) facility in biological safety cabinets in accordance with protocols approved by the Vanderbilt University Department of Environment, Health, and Safety and the Vanderbilt Institutional Biosafety Committee. The three SL15649 replicon system plasmids were linearized by digestion with NotI-HF, purified by phenol-chloroform extraction, and used as templates in transcription reactions using an mMessage mMachine SP6 transcription kit (Life Technologies) to produce capped, full-length RNA transcripts *in vitro*. Viral RNA transcripts were introduced into BHK21 cells by electroporation using a GenePulser electroporator. Culture supernatants containing VRPs were collected 24 hours after electroporation; supernatants were clarified by centrifugation at 855 × g for 20 min, aliquoted, and stored at -80 °C. VRP stocks were evaluated for propagation-competent recombinant virus by serial passage of 20% of the stock and 10% of passage 1 culture supernatant using Vero81 cells, which were examined for cytopathic effect (CPE) 72 hours after infection. Stocks were considered to have passed this safety test when CPE was not detected in the final passage. Stocks were then removed from the BSL3 laboratory.

VRP neutralization and GFP reporter assay. Vero 81 cells (2.25×10^3 cells/well) were seeded into wells of 384-well plates and incubated at 37°C for 24 hours. Neat hybridoma supernatant or serial dilutions of purified mAbs were incubated with VRPs at an MOI of ~ 5 infectious units/cell in virus dilution buffer (VDB; RPMI medium containing 20 mM HEPES supplemented to contain 1% FBS) at 37°C for 1 hour and then adsorbed to cells. Cells were incubated at 37°C for 18 hours, stained with Hoechst stain to label nuclei, and

imaged using an ImageXpress Micro XL imaging system (Molecular Devices) at the Vanderbilt High-Throughput Screening Facility. Total and CHIKV-infected cells (marked by GFP expression) were quantified using MetaXpress software (Molecular Devices) in two fields of view per well. For each antibody, EC_{50} values with 95% confidence intervals were determined using nonlinear regression to fit separate logistic growth curves using the R statistics program (R.C. Team, 2014).

Virus stocks prepared as antigen for ELISA. The infectious clone plasmid for CHIKV vaccine strain 181/25 (Levitt *et al.,* 1986 and Mainou *et al.,* 2013) was linearized with NotI-HF and transcribed *in vitro* using an mMessage mMachine SP6 transcription kit (Life Technologies). Viral RNA was introduced into BHK21 cells by electroporation. Culture supernatants were harvested 24 hours later, clarified by centrifugation at 855 × g for 20 min, aliquoted, and stored at -80°C.

Virus capture ELISA for hybridoma screening. Antibody binding to virus particles was performed by coating assay plates with purified mouse mAb CHK-187 (Pal *et al.,* 2013), prepared at 1 μg/mL in 0.1 M Na_2CO_3 and 0.1 M $NaHCO_3$ pH 9.3 binding buffer, was used to coat ELISA plates (Nunc 242757) and incubated at 4°C overnight. After incubating plates for 1 hour with blocking buffer (1% powdered milk and 2% goat serum in PBS with Tween 20 [PBS-T]), plates were washed five times with PBS-T and incubated with 25 μL of culture supernatant from BHK21 cell monolayers infected with CHIKV vaccine strain 181/25. After incubation at room temperature for 1 hour, plates were washed ten times with PBS, and 10 μL of B cell culture supernatant was added into 25 μL/well of blocking buffer. Plates were incubated at room temperature for 1 hour prior to washing five times with PBS-T. A secondary antibody conjugated to alkaline phosphatase (goat anti-human Fc; Meridian Life Science, W99008A) was applied at a 1:5,000 dilution in 25 μL/well of blocking buffer, and plates were incubated at room temperature for 1 hour. Following five washes with PBS-T, phosphatase substrate solution (1 mg/mL phosphatase substrate in 1 M Tris aminomethane [Sigma, S0942]) was added at 25 μL/well, and plates were incubated at room temperature for 2 hours before determining the optical density at 405 nm using a Biotek plate reader.

CHIKV-specific control human mAbs. In some assays, two previously described human CHIKV-specific mAbs, 5F10 and 8B10 (Warter *et al.,* 2011), were used as positive controls. These mAbs were expressed in 293F cells (Invitrogen) following transfection with an IgG1 expression plasmid (Lonza) containing a sequence-optimized cDNA of the 5F10 and

8B10 antibody variable gene regions based on sequences provided by Cheng-I Wang and Alessandra Nardin (Singapore Immunology Network, A*STAR, Singapore).

ELISA for mAb binding to E2 protein. Recombinant CHIKV E2 ectodomain protein (corresponding to the CHIKV-LR2006 strain) was generated in *E. coli* as described (Pal *et al.*, 2013) and adsorbed to microtiter plates (100 µL of a 2 µg/mL E2 protein solution in 0.1 M Na_2CO_3, 0.1 M $NaHCO_3$, and 0.1 % NaN_3 [pH 9.3]) at 4°C overnight. Plates were rinsed three times with PBS containing 0.05% Tween-20, and incubated at 37 °C for 1 hour with blocking buffer (PBS, 0.05% Tween-20, and 2% [w/v] of BSA). Primary human mAb (diluted to 10 µg/mL in blocking buffer) was added to wells at room temperature for 1 hour. Plates were rinsed three times with PBS containing 0.05% Tween-20, and secondary antibody (biotin-conjugated goat anti-human IgG (H and L chains) with minimal cross-reactivity to mouse serum proteins (Jackson ImmunoResearch Laboratories) diluted 1/20,000 in blocking buffer) and streptavidin-conjugated horseradish peroxidase (diluted in PBS with 0.05% Tween-20; Vector Laboratories) were added sequentially, each at room temperature for 1 hour with plate rinsing in between steps. After four rinses with PBS, plates were incubated at room temperature with 100 µL of TMB (3,3′,5,5′-tetramethylbenzidine) chromogenic substrate solution (Dako) for 5 min, and the reaction was stopped by addition of 2 N H_2SO_4. Product intensity was determined using an ELISA plate reader at an optical density of 450 nm.

Affinity measurements by surface plasmon resonance. Interactions of purified human mAbs and CHIKV proteins were analyzed kinetically using a Biacore T100 instrument as described (Austin *et al.*, 2012). *For the intact IgG with soluble CHIKV p62-E1*, anti-human IgG antibodies (GE Life Sciences) were immobilized onto a Series S CM5 chip and used to capture anti-CHIKV or control (hu-WNV E16) antibodies. The CHIKV p62-E1 was injected over the surface at 65 µL/min for 180 sec and allowed to dissociate for 1000 sec before regeneration with 3 M $MgCl_2$ between cycles. Some antibodies did not bind to the monomeric E1 protein, therefore the inventors tested them for binding to VLPs. *For the kinetic measurements with the CHIKV VLP*, anti-mouse IgG antibodies (GE Life Sciences) were immobilized to capture a set of mouse anti-CHIKV antibodies with sub-nanomolar affinities, which were in turn used to capture the CHIKV VLPs. Anti-CHIKV IgG or Fab was injected over the chip surface at 65 µL/min for 180 sec and allowed to dissociate for 1000 sec before regeneration with 10 mM glycine pH 1.7 between cycles. All data were processed using the Biacore Evaluation Software (Version 1.1.1) and a global 1:1 Langmuir fit of the curves. Results were obtained from at least three independent experiments.

Virus strains used in focus reduction neutralization tests. To determine mAb breadth and neutralization potency, the inventors used four representative strains with at least one representative from each CHIKV genotype, including one prototype virus from each of the three genotypes and also a strain from the current Caribbean outbreak. Strain LR2006_OPY1 (LR) (CHIKV East/Central/South African [ECSA] genotype) was provided by Stephen Higgs (Manhattan, KS). Strain NI 64 IbH 35 (West African genotype) and strains RSU1 and 99659 (Asian genotype; isolated in 2014 from a subject in the British Virgin Islands (Lanciotti & Valadere, 2014)) were provided by Robert Tesh (World Reference Center for Emerging Viruses and Arboviruses, Galveston, TX).

Focus reduction neutralization test (FRNT) with infectious CHIKV. Serial dilutions of purified human mAbs were incubated with 100 focus-forming units (FFU) of CHIKV at 37°C for 1 hour. MAb-virus complexes were added to Vero cells in 96-well plates. After 90 min incubation, cells were overlaid with 1% (w/v) methylcellulose in Modified Eagle Media (MEM) supplemented to contain 2% FBS. Cells were incubated for 18 hours and fixed with 1% paraformaldehyde in PBS. Cells were incubated sequentially with 500 ng/mL of murine CHK-11 (Pal *et al.,* 2013) and horseradish peroxidase (HRP)-conjugated goat anti-mouse IgG in PBS supplemented to contain 0.1% saponin and 0.1% bovine serum albumin (BSA). CHIKV-infected foci were visualized using TrueBlue peroxidase substrate (KPL) and quantified using an ImmunoSpot 5.0.37 macroanalyzer (Cellular Technologies Ltd). EC_{50} values were calculated using nonlinear regression analysis after comparison to wells inoculated with CHIKV in the absence of antibody.

Biolayer interferometry competition binding assay. CHIKV-LR2006 E2 ectodomain protein containing a polyhistidine-tag (20 µg/mL) was immobilized onto Anti-Penta-His biosensor tips (ForteBio #18-5077) for 2 min. After determining the baseline signal in kinetics buffer (KB, 1X PBS, 0.01% BSA and 0.002% Tween 20) for 1 min, biosensor tips were immersed into wells containing primary antibody at a concentration of 100 µg/mL for 5 min and then immersed into wells containing competing mAbs at a concentration of 100 µg/mL for 5 min. The percent binding of the competing mAb in the presence of the first mAb was determined by comparing the maximal signal of the competing mAb applied after the initial mAb complex to the maximal signal of competing mAb alone. Antibodies were judged to compete for binding to the same site if maximum binding of the competing mAb was reduced to < 30% binding affinity alone. Antibodies were considered non-competing if maximum binding of the competing mAb was > 70% of non-competed binding. A level of 30-70% of non-competed binding was considered intermediate competition.

Mutagenesis epitope mapping. A CHIKV envelope protein expression construct (strain S27, Uniprot Reference #Q8JUX5) with a C-terminal V5 tag was subjected to alanine-scanning mutagenesis to generate a comprehensive mutation library. Primers were designed to mutate each residue within the E2, 6K, and E1 regions of the envelope proteins (residues Y326 to H1248 in the structural polyprotein) to alanine; alanine codons were mutated to serine (Fong *et al.*, 2014). In total, 910 CHIKV envelope protein mutants were generated (98.5% coverage), sequence confirmed, and arrayed into 384-well plates. HEK-293T cells were transfected with the CHIKV mutation library in 384-well plates and incubated for 22 hours. Cells were fixed in 4% paraformaldehyde (Electron Microscopy Sciences) in PBS plus calcium and magnesium (PBS+/+) and stained with purified mAbs at 0.25 to 1.0 µg/mL or purified Fab fragments at 2.5 µg /mL diluted in 10% normal goat serum (NGS; Sigma). Primary antibody concentrations were determined using an independent immunofluorescence titration curve against wild-type CHIKV envelope proteins to ensure that signals were within the linear range of detection. Antibodies were detected using 3.75 µg/mL AlexaFluor488-conjugated secondary antibody (Jackson ImmunoResearch Laboratories) in 10% NGS. Cells were washed twice with PBS without magnesium and calcium (PBS -/-) and resuspended in Cellstripper (Cellgro) with 0.1% BSA (Sigma). Mean cellular fluorescence was detected using a high-throughput flow cytometer (HTFC, Intellicyt). Antibody reactivity against each mutant clone was calculated relative to wild-type protein reactivity by subtracting the signal from mock-transfected controls and normalizing to the signal from wild-type-transfected controls. Amino acids were identified as required for mAb binding if the corresponding alanine mutant did not react with the test mAb but did react with other CHIKV antibodies. This counter-screen strategy facilitates the exclusion of mutants that are misfolded or have an expression defect (Christian *et al.*, 2013, Paes *et al.*, 2009 and Selvarajah et al., 2013). Amino acids required for antibody binding were visualized on the CHIKV envelope protein crystal structure (monomer PDB ID #3N41 and trimer PDB ID #2XFB) using PyMol software.

Pre- and post-attachment neutralization assays. Vero 81 cells (ATCC CCL-81; ~ 7.5×10^3 cells/well) were seeded into wells of 96-well plates and incubated at 37°C for ~ 24 hours. For pre-attachment assays, dilutions of mAb were prepared at 4°C in virus dilution buffer (VDB) and pre-incubated with VRPs at 4°C for 1 hour. Antibody-virus complexes were added to pre-chilled Vero 81 cells at 4°C for 1 hour. Non-adsorbed virus was removed by three washes with VDB, and cells were incubated in complete medium at 37°C for 18 hours. The post-attachment assay was performed similarly, except that an equivalent MOI of VRPs was first adsorbed to Vero 81 cells at 4 °C for 1 hour, unbound VRPs were removed by

three washes with virus dilution buffer, and cells were incubated with pre-chilled VDB containing serial dilutions of mAb at 4°C for 1 hour. Unbound mAbs were removed by three washes with VDB, and cells were incubated in complete medium at 37°C for 18 hours. Cells were stained, imaged, and analyzed as described for VRP neutralization assays, with four fields of view per well, yielding a total of ~ 800 to 1,000 cells analyzed for GFP expression per sample.

Fusion inhibition assays. Virus fusion with the plasma membrane was assessed using an FFWO assay (Edwards & Brown, 1986). Vero 81 cells (~ 3.75×10^3 cells/well) were seeded into wells of 96-well plates and incubated at 37°C for ~ 24 hours. Cells were washed once with binding medium (RPMI 1640 supplemented to contain 1% FBS, 25 mM HEPES [pH 7.4] and 20 mM NH_4Cl to prevent infection through endosomal fusion) and incubated in binding medium at 4°C for 15 min. Inoculum containing VRPs was diluted in binding medium and incubated with cells at 4°C for 1 hour. Unbound VRPs were removed by two washes with binding medium. Serial dilutions of mAbs in VDB were incubated with cells at 4°C for 1 hour, and unbound mAb was removed by two washes with VDB. FFWO was induced by the addition of pre-warmed fusion medium (RPMI 1640, 1% FBS, 25 mM HEPES, and 30 mM succinic acid at pH 5.5) at 37°C for 2 min. In parallel wells, control medium (RPMI 1640, 1% FBS, 25 mM HEPES at pH 7.4) was added at 37°C for two min. The medium was removed and cells were incubated in DMEM supplemented to contain 5% FBS, 20 mM NH_4Cl (to ensure that infection occurred only through pH-dependent plasma membrane fusion), and 25 mM HEPES [pH 7.4]). At 18 hours post infection, cells were stained, imaged, and analyzed as described, with four fields of view per well, yielding a total of ~ 800 - 1,000 cells analyzed for GFP expression per sample.

***In vivo* protection studies in mice.** This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The protocols were approved by the Institutional Animal Care and Use Committee at Washington University School of Medicine (Assurance Number: A3381-01). *Ifnar*$^{-/-}$ mice were bred in pathogen-free animal facilities at Washington University School of Medicine, and infection experiments were performed in A-BSL3 facilities with the approval of the Washington University Animal Studies Committee. Footpad injections were performed under anesthesia that was induced and maintained with ketamine hydrochloride and xylazine. For prophylaxis studies, human mAbs were administered by intraperitoneal injection to 6 week-old *Ifnar*$^{-/-}$ mice 1 day prior to subcutaneous inoculation in the footpad with 10 FFU of CHIKV-LR diluted in HBSS with 1%

heat-inactivated FBS. For therapeutic studies, 10 FFU of CHIKV-LR was delivered 24, 48, or 60 hours prior to administration of a single dose of individual or combinations of human mAbs at specified doses.

Example 2 - Results

Isolation of CHIKV-specific human mAbs. The inventors isolated a panel of mAbs from a single individual who acquired CHIKV infection in Sri Lanka in 2006 and presented with fever, arthralgias, and rash (FIG. 4). The clinical course and B cell transformation and screening procedures are provided in the Online Methods. They transformed B cells in two separate experiments from a single blood sample collected from the donor five and a half years following natural infection. They observed a virus-specific B cell frequency of approximately 1 in 1,000 total B cells and established 30 stable hybridomas from B cell lines secreting antibodies that bound to virus. The mAb panel contained IgGs of multiple subclasses, with 24 IgG1, three IgG2, and two IgG3; one was not determined due to poor hybridoma growth (Table 5).

Assessment of mAb neutralization. Eighteen of the mAbs exhibited neutralizing activity against Asian CHIKV strain SL15649-GFP virus reporter particles (VRPs) with EC_{50} values < 40 ng/mL, with eleven exhibiting ultrapotent inhibitory activity (defined as EC_{50} values < 10 ng/mL, Table 5). Four mAbs possessed weak inhibitory activity (EC_{50} values in the 0.1 to 5 μg/mL range), and eight of the mAbs had no inhibitory activity at the highest concentration tested (EC_{50} values > 10 μg/mL).

Breadth of neutralizing activity. The inventors determined the EC_{50} values for each antibody against representative infectious CHIKV strains of the East/Central/South African (ECSA) genotype (LR2006 OPY1 [LR] strain), the West African genotype (NI 64 IbH 35 strain), and the Asian genotype (RSU1 and 99659 [2014 Caribbean] strains) using a high-throughput focus reduction neutralization test (FRNT) (Pal *et al.*, 2013). Twenty-five of the mAbs exhibited neutralizing activity against at least one CHIKV strain (EC_{50} values < 10 μg/mL), with eight mAbs exhibiting neutralization in a potent range (EC_{50} values between 10 – 99 ng/mL), and thirteen mAbs exhibiting neutralization in an ultrapotent range (EC_{50} values < 10 ng/mL) (Table 5). For comparative purposes, the inventors also tested the previously reported human mAbs 5F10 and 8B10 against viruses of all three genotypes, and in every case the EC_{50} values were >100 ng/mL (range 161-1337). In most cases, the mAbs the inventors isolated exhibited relatively similar neutralizing activity against virus from all three

genotypes. Six mAbs (2B4, 2H1, 4J21, 4N12, 5M16, and 9D14) inhibited viruses from all three genotypes with ultrapotent activity (EC_{50} values < 10 ng/mL). These data indicate that a single individual can develop multiple CHIKV-specific antibodies that are ultrapotent and broadly neutralizing.

Binding to E2 protein. The CHIKV E2 protein is a dominant target of murine (Goh *et al.*, 2013; Lum *et al.*, 2013), nonhuman primate (Kam *et al.*, 2014), and human (Fong *et al.*, 2014; Kam *et al.*, 2012a; Kam *et al.*, 2012b; Selvarajah *et al.*, 2013) humoral responses. The inventors tested the human mAbs for binding to a monomeric form of the ectodomain of E2 protein expressed in E. coli (Pal *et al.*, 2013). Nine mAbs bound strongly to the E2 ectodomain, six exhibited moderate binding, one bound weakly, and 14 failed to bind above background (Table 5). The capacity to bind purified E2 protein *in vitro* did not correlate directly with neutralizing potency (Table 5). A subset of 17 human mAbs was tested using a surface plasmon resonance assay for binding to the p62-E1 protein derived from mammalian cells (Voss *et al.*, 2010). All mAbs bound in the nM range, with K_D values from 0.5 to 20 nM. Differences in binding kinetics did not correlate with antigenic specificity or functional activity (Table S1).

Competition-binding studies. To identify non-overlapping antigenic regions in recombinant E2 protein recognized by different neutralizing mAbs, the inventors used a quantitative competition-binding assay. For comparison, they also evaluated four previously described murine mAbs (CHK-84, CHK-88, CHK-141, and CHK-265) (Pal *et al.*, 2013) and the previously described human mAb 5F10 (Warter *et al.*, 2011) (FIG. 5). The pattern of competition was complex, but three major competition groups were evident, which the inventors designated group 1 (red box), group 2 (blue boxes) or group 3 (green box). The inventors also defined a fourth group containing the single human mAb, 5F19 (orange box). These competition studies suggest that there are three major antigenic regions recognized by CHIKV-specific antibodies.

Epitope mapping using alanine-scanning mutagenesis. The inventors used an alanine-scanning mutagenesis library coupled with cell-based expression and flow cytometry to identify amino acids in E2 and E1 proteins of CHIKV strain S27 (ECSA genotype) required for antibody binding (Fong *et al.*, 2014) (FIGS. 6A-F). Residues required for antibody binding to CHIKV glycoproteins for a subset of 20 human mAbs are listed in Table 6. Mutations affecting binding of these 20 mAbs are indicated in an alignment of the full-length E2 sequences of strain S27 and strains representing all CHIKV genotypes that were used in this study (FIG. 1A). The amino acids in E2 that influence binding are located

primarily in the solvent-exposed regions of domains A and B and arches 1 and 2 of the β-ribbon connector, which links domains A and B (Voss *et al.*, 2010) (FIG. 1A). Comparison of the antigenic sites identified by loss-of-binding experiments using alanine-scanning mutagenesis with the competition binding analysis (FIG. 5) demonstrated that competition groups 1 and 2 generally corresponded to sites within domain A and the arches, whereas group 3 corresponded to regions in domain B.

Structural analysis of antigenic regions. A large and diverse number of the surface residues in domains A and B and the arches are contacted by at least one of the mAbs (FIGS. 1B-C). Two principal antigenic regions in E2 accounted for the binding of multiple mAbs. The first region is located in domain A, between amino acids 58 and 80, and contains the putative receptor-binding domain (RBD) (Sun *et al.*, 2014; Voss *et al.*, 2010). The second region is located in domain B, between amino acids 190 and 215. Both sequence regions project away from the viral envelope and are located near the E2 trimer apex (FIGS. 6A-F and 7).

Mechanism of neutralization. The inventors conducted pre- and post-attachment neutralization assays using mAbs displaying a range of inhibitory activities. As expected, all five mAbs tested neutralized infection efficiently when pre-incubated with VRPs (FIG. 2A). However, mAb 4B8 did not neutralize VRPs completely even at high concentrations, suggesting the presence of a fraction of CHIKV virions resistant to this mAb; this pattern also was observed in assays using viable CHIKV strains corresponding to the three distinct CHIKV genotypes (data not shown). In contrast, mAbs 3E23, 4J21, 5M16, and 9D14 completely neutralized infection when administered before attachment. All five human mAbs also neutralized CHIKV infection when added following attachment, but the inventors observed three different patterns of activity (FIG. 2A). MAb 4B8 was incapable of complete neutralization when added post-attachment, and the fraction of resistant virions was larger compared with that observed following pre-attachment neutralization. MAb 9D14 neutralized VRPs with comparable efficiency whether added before or after attachment. MAbs 3E23, 4J21, and 5M16 displayed complete neutralization of VRPs, but the efficiency of neutralization post-attachment was lower than that following pre-attachment. The mAbs 2H1 and 4N12 also efficiently neutralized VRPs when added prior to or after attachment (FIG. 8).

Fusion-from-without (FFWO) assay testing of five of the ultrapotently neutralizing mAbs (3E23, 4B8, 4J21, 5M16, or 9D14) revealed that all inhibited fusion (Edwards and Brown, 1986). As expected, when virions pre-treated with mAbs were incubated continuously with medium buffered at neutral pH, little to no infection was observed (FIG.

2B). In the absence of antibody treatment, a short pulse of acidic pH-buffered medium resulted in infected cells, indicating fusion between the viral envelope and plasma membrane. Notably, all five human mAbs inhibited plasma membrane fusion and infection, with mAb 9D14 exhibiting the greatest potency in this assay. These studies suggest that ultrapotently neutralizing mAbs block CHIKV fusion.

MAb prophylaxis *in vivo*. The inventors tested a subset of mAbs exhibiting diverse levels of neutralizing activity (Table 7) in a lethal infection model with 6-week-old, highly immunodeficient Ifnar$^{-/-}$ mice. Mice were pre-treated with a single 50 μg dose (~ 3 mg/kg) of human anti-CHIKV mAbs or a West Nile virus-specific isotype control mAb (WNV hE16) 24 hours before subcutaneous injection with a lethal dose of CHIKV-LR2006. All mice treated with the isotype control mAb succumbed to infection by 4 days post-inoculation. Pretreatment with mAbs 4B8, 4J21, or 5M16 completely protected Ifnar$^{-/-}$ mice, whereas treatment with mAbs 3E23 or 9D14 partially protected the infected animals, with 67% survival rates (FIG. 3A). Surprisingly, mAb 2D12, which weakly neutralized in vitro, protected 83% of the animals.

MAb post-exposure therapy *in vivo*. Ifnar$^{-/-}$ mice were inoculated with a lethal dose of CHIKV-LR2006 and then administered a single 50 μg (~ 3 mg/kg) dose of representative mAbs 24 hours following virus inoculation. Therapeutic administration of these mAbs provided complete protection, whereas the isotype-control mAb provided no protection (FIG. 3B). To define further the therapeutic window of efficacy, Ifnar$^{-/-}$ mice were administered a single 250 μg (~14 mg/kg) dose of representative mAbs 48 hours after challenge with CHIKV-LR2006. Treatment with 5M16, 4J21, and 4B8 protected 85%, 50%, and 12.5% of the animals, respectively (FIG. 3C). Remarkably, monotherapy with 4N12 at the later time point of 60 hours protected 100% of animals when used at a dose of 500 μg, (~28 mg/kg) (FIG. 3D). These data establish that human mAbs can protect against CHIKV-induced death, even at intervals well after infection is established.

Analogously, studies were performed in WT mice to assess the effects of human mAbs on CHIKV acute and chronic arthritis. MAbs were administered on day 1 or 3 after infection and viral burden or RNA was analyzed at D3, 5 or 28 after infection. Depending on the tissue and time examined either 1H12 or 4J14 provide the most significant virological protection. 4N12 also provided significant protection in these assays.

Combination mAb therapy *in vivo*. Given the possibility of resistance selection in vivo in animals treated with a single anti-CHIKV mAb (Pal *et al.*, 2013), the inventors tested whether a combination of two anti-CHIKV human mAbs could protect mice against lethal

challenge. They chose pairs of neutralizing mAbs based on the potency of individual mAbs *in vitro*. Ifnar$^{-/-}$ mice were administered a single combination antibody treatment dose (250 μg of each, ~ total of 28 mg/kg) of the most effective mAbs 60 hours after inoculation. Although some mAb combinations ([4J21 + 2H1] and [4J21 + 5M16]) provided little or no protection, others ([4J21 + 4N12]) resulted in a 63% survival rate at this very late time point (FIG. 3D). Thus, combination mAb therapy protected against lethal CHIKV infection in highly immunocompromised mice even when administered within 24 to 36 hours of when these animals succumb. In this setting, 4N12 worked less well in combination with 4J21 than it did as monotherapy, although the dosing of 4N12 in monotherapy experiments (500 μg) was twice that of the 4N12 component in combination therapy (250 μg).

Table S1. Kinetics of human CHIKV antibodies binding antigen measured by SPR

Values for ka, kd, KD are means ± standard deviations. KD = kd/ka; $t_{1/2}$ = (ln(2)/kd)/60.

CHKV MAb	Ligand	ka (10^5 M-1s-1)	kd (10^{-4} s-1)	KD (nM)	$t_{1/2}$ (min)
5M18	pE2-E1	1.09 ± 0.02	1.13 ± 0.02	1.03 ± 0.01	102 ± 2
5M18 Fab	VLP	1.19 ± 0.01	0.84 ± 0.15	7.07 ± 1.06	137 ± 31
4J21	pE2-E1	1.19 ± 0.02	0.82 ± 0.04	0.54 ± 0.01	169 ± 11
4J21 Fab	VLP	1.58 ± 0.03	14.2 ± 0.29	9.03 ± 0.03	8 ± 0.2
3E23	pE2-E1	3.18 ± 2.43	2.67 ± 0.87	8.11 ± 5.41	43 ± 19
3E23 Fab	VLP	0.203 ± 0.03	3.93 ± 0.40	19.6 ± 3.16	29 ± 3
4B6	pE2-E1	2.98 ± 2.98	5.06 ± 1.19	5.57 ± 1.19	23 ± 3
4B6 Fab	VLP	0.60 ± 0.04	3.39 ± 0.30	5.60 ± 0.46	35 ± 3
5N20	pE2-E1	2.98 ± 0.75	2.40 ± 0.66	0.87 ± 0.37	48 ± 17
1L1	pE2-E1	0.88 ± 0.44	2.79 ± 0.36	3.79 ± 2.10	42 ± 8
2C2	pE2-E1	1.54 ± 0.65	8.08 ± 1.45	4.59 ± 2.32	19 ± 6
2D12	pE2-E1	17.6 ± 1.64	6.41 ± 4.97	0.49 ± 0.08	13 ± 4
4N12	pE2-E1	1.24 ± 0.02	1.19 ± 0.01	0.95 ± 0.02	98 ± 1
5O14	pE2-E1	0.79 ± 0.02	9.11 ± 0.19	1.15 ± 0.01	13 ± 0.3
6D14	pE2-E1	2.78 ± 0.90	3.82 ± 0.14	1.13 ± 0.40	41 ± 2
6G18	pE2-E1	3.90 ± 0.11	1.88 ± 0.11	0.48 ± 0.02	62 ± 3
4J14	pE2-E1	1.81 ± 0.47	15.3 ± 2.52	9.94 ± 2.64	8 ± 1
5F	pE2-E1	2.61 ± 0.04	50.9 ± 0.75	19.5 ± 0.2	2 ± 0.03
3A2	pE2-E1	2.12 ± 0.02	10.1 ± 0.12	4.78 ± 0.08	11 ± 0.1
1M9	pE2-E1	1.88 ± 0.99	3.90 ± 0.36	2.48 ± 0.99	29 ± 2
3B4	pE2-E1	2.91 ± 0.09	1.88 ± 0.11	0.64 ± 0.03	74 ± 5
8B	pE2-E1	0.99 ± 0.03	2.74 ± 0.10	2.77 ± 0.18	42 ± 2
8E22	pE2-E1	0.46 ± 0.02	2.0 ± 0.13	4.22 ± 0.42	58 ± 4

Example 3 – Discussion

The inventors report the isolation of a diverse panel of naturally-occurring human mAbs from a single individual, the majority of which recognize the CHIKV E2 protein and display remarkable neutralizing activity *in vitro* and therapeutic efficacy *in vivo*. As a class, the most inhibitory antibodies also exhibited broad activity, neutralizing viruses from all three CHIKV genotypes, including a strain currently circulating in the Caribbean. The majority of human CHIKV-specific mAbs isolated in this study neutralized the virus at concentrations less than 100 ng/mL, and many exhibited inhibitory activity at less than 10 ng/mL. This activity is greater than the inventors have observed in previous studies of human mAbs against other pathogenic human viruses, including H1, H2, H3, or H5 influenza viruses (Hong *et al.*, 2013; Krause *et al.*, 2012; Krause *et al.*, 2011a; Krause *et al.*, 2011b; Krause *et al.*, 2010; Thornburg *et al.*, 2013; Yu *et al.*, 2008), dengue viruses (Messer *et al.*, 2014; Smith *et al.*, 2013a; Smith *et al.*, 2014; Smith *et al.*, 2013b; Smith *et al.*, 2012), and others. The potency of many human CHIKV mAbs is comparable to or exceeds that of best-in-class murine neutralizing CHIKV mAbs (Fong *et al.*, 2014; Fric *et al.*, 2013; Pal *et al.*, 2013; Warter *et al.*, 2011), which were generated after iterative boosting and affinity maturation. Most other neutralizing human mAbs against CHIKV are substantially less potent (Fong *et al.*, 2014; Selvarajah *et al.*, 2013; Warter *et al.*, 2011). A single previously reported human CHIKV-specific mAb (IM-CKV063) displays activity comparable to the ultrapotent neutralizing mAbs reported here (Fong *et al.*, 2014).

The inventors observed a diversity of epitope recognition patterns in E2 by the different neutralizing CHIKV mAbs tested. Fine epitope mapping with alanine-substituted CHIKV glycoproteins showed that recognition of three structural regions in E2 is associated with mAb-mediated neutralization: domain A, which contains the putative RBD (Sun *et al.*, 2013; Voss *et al.*, 2010), domain B, which contacts and shields the fusion loop in E1 (Voss *et al.*, 2010), and arches 1 and 2 of the β-ribbon connector, which contains an acid-sensitive region and links domains A and B (Voss *et al.*, 2010). Of the antibodies mapped to epitopes in E2, the bulk (those in competition groups 1 and 2) preferentially recognized sites in domain A and arches 1 and 2, whereas a smaller group (in competition group 3) recognized sites in domain B. These data suggest that surface-exposed regions in domain A and the arches are dominant antigenic sites that elicit human neutralizing antibody responses. The inventors conclude that the highly conserved region in domain A and arch 2 might elicit a

broadly protective immune response and serve as an attractive candidate for epitope-focused vaccine design.

Remarkably, almost a quarter of surface-exposed residues in the critical E2 domains appear to be engaged by one or more mAbs from a single individual. The existence of functionally diverse binding modes on the major antigenic sites is implied by two observations: (a) some mAbs bound to similar epitopes but exhibited inhibitory activity that varied by several orders of magnitude and (b) there was little correlation between neutralization capacity and affinity of binding to E2 protein. Seven of the most potently neutralizing human mAbs (2H1, 3E23, 4B8, 4J21, 4N12, 5M16, and 9D14) inhibited CHIKV infection at a step following attachment, likely via prevention of pH-dependent structural changes, which prevents nucleocapsid penetration into the cytoplasm (Kielian *et al.*, 2010).

As therapeutic efficacy in mice appears to predict treatment outcomes in experimentally-induced infection and arthritis in nonhuman primates (Pal *et al.*, 2013; Pal *et al.*, 2014), the data here suggest that prophylaxis of humans with CHIKV-specific human mAbs would prevent infection. Given concerns about selection of resistant variants with monotherapy (Pal *et al.*, 2013), combination therapy using ultrapotent neutralizing antibodies that target different regions of E2 may be desirable. Patient populations at markedly increased risk of severe disease could be targeted during outbreaks, including those with serious underlying medical conditions (*e.g.*, late-term pregnant women, the immunocompromised, and the elderly). Further clinical testing is planned to determine whether neutralizing human mAbs can prevent or ameliorate established joint disease in humans.

TABLE 1 – NUCLEOTIDE SEQUENCES FOR ANTIBODY VARIABLE REGIONS

Clone	Variable Sequence Region	SEQ ID NO:
1H12 heavy	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTG AAGGTCTCCTGCAAGGCCTCTGGTTACAGCTTTACCAGCTACGGTATCAGCTGG GTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCACTTAC AAAGGTTACACACAGTATGCACAGAACTTCCAGGGCAGAGTCACCATCACCACA GACACACCCGCGACTACAGTCTATATGGAGCTGAGGAGCCTGAGATCTGACGAC ACGGCCGTGTATTACTGCGCGAGAGTTCTTTCCGAGACTGGTTATTTCTACTAC TACTACTACGGTATGGACGTCTGGGGCCAAGGGACCCTGGTCACCGTCTCCTCA	2
1H12 light	CAGGCTGTGGTGACTCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAGGGTC ACCATCTCCTGTACTGGGAGCAGCTCCAACATCGGGGCAGATTATAATGTACAC TGGTACCAGCTGCTTCCAGGAACAGCCCCCAAACTCCTCATCTATGGTAACACC AATCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCA GCCTCCCTGGCCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGC CAGTCCTATGACAGCAGCCTGAGTGCTTCGGTATTCGGCGGAGGGACCAAACTG ACCGTCCTAG	3

2B4 heavy	caggtgcagctggtgcaatctgggtctgagttgaagaagcctgggGCCTCAGTG AAGGTCTCCTGCAAGGCTTCTGGATACAGTTTCACTAGCTATTCTATCAACTGG GTGCGACAGGCCCCTGGACAAGGGCCTGAGTGGATGGGATGGATCGACACCAAC ACTGGGAACCCAACCTATGCCCAGGACTTCGCAGGACGGTTTGTCTTCTCCTTG GACACCTCTGTCACCACGGCATATCTGCAGATCAGCAGCCTAAAGGCTGGGGAC ACTGCCGTTTATTACTGTGCAACATATTATGTTGACCTTTGGGGGAGTTATCGC CAAGACTACTACGGTATGGACGTCTGGGGCCAC	4
2B4 light	cagtctgtgctgactcagccaccctcagcgtctgggacccccgggcagagggtc accatCTCTTGTTCTGGAGGGAGCTCCAACATCGGGAGTAATCCTGTAAATTGG TACCAGATGGTCCCAGGAACGGCCCCCAAACTCCTCCTCTATACTAATAATCAG CGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCC TCCCTGGCCATCAATGGACTCCAGTCTGAGGATGAGGCTGATTATTACTGTGCA GTATGGGATGACAGCCTGAGTGGCCGTTGGGTGTTCGGCGGAGGGACCAAGGTG ACCGTCCTA	5
2H1 heavy	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTG AGGGTCTCCTGCAAGGCGTCTGGTTACACCTTTACCAGTTATGGTATCAGCTGG GTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCACTTAC AATGGTGACACAAACTATGCACAGAAGTTCCAGGGCAGAGTCACCTTGACAACA GAGACATCCACGAGCACAGCCTACATGGAGCTGAGGCGCCTGAGATCTGACGAC ACGGCCGTTTACTACTGTGCGAGAGATTTTGAATTTCCCGGAGATTGTAGTGGT GGCAGCTGCTACTCCAGGTTCATCTACCAGCACAACGACATGGACGTCTGGGGC CACGGGACCCTGGTCACCGTCTCCTCAGCAAGC	6
2H1 light	CAGGCTGTGGTGACTCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTC ACCATCTCCTGCTCTGGAAGCAGCTCCAACATTGGGAATCATTATGTATCCTGG TACCAGCACCTCCCGGGAACAGCCCCCAAACTCCTCATTTATGACAATTATAAG CGACCCTCAGTGATTCCTGACCGATTCTCTGCCTCCAAGTCTGGCGCGTCAGCC ACCCTGGGCATCATCGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGA ACATGGGATAGCAGCCTGAGTGCTGTGGTATTCGGCGGAGGGACCAAGCTGACC GTCCTA	7
3E23 heavy	CAGGTGCAGCTGGTGCAGTCGGGCCCAGGACTGGTGAAGCCTTCGGACACCCTG TCCCTCACCTGCAGTGTCTCAAGTGACGCCCTCCGCAGCAGGAGTTATTACTGG GGCTGGGTCCGCCAGCCCCCCGGGAAGGGATTGGAGTGGATTGGGACTGTCTCT TATAGTGGGGGCACCTACTACAACCCGTCCCTCCAGAGTCGAGTCACCGTGTCG GTGGACACGTCCAAGAACCACTTCTCCCTGAGGTTGAACTCTGTGACCGCCGCA GACGCGGCTGTTTATTACTGTGCGAGATCTTATTTCTATGATGGCAGTGGTTAC TACTACCTGAGCTACTTTGACTCCTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA	8
3E23 light	CAGGCTGTGGTGACTCAGGAGCCCTCACTGACTGTGTCCCCAGGAGGGACAGTC ACTCTCACCTGTGCTTCCAGCACTGGAGCAGTCACCAGTGGTCACTATCCAAAC TGGTTCCAGCAGAAACCTGGACAACCACCCAGGGCCCTGATTTATAGCACAGAC AACAAGCACTCCTGGACCCCTGCCCGGTTCTCAGGCTCCCTCCTAGGGGTCAAG GCTGCCCTGACACTGTCAGATGTACAGCCTGAGGACGAGGCTGACTATTACTGC CTGCTCCATTTTGGTGGTGTCGTGGTCTTCGGCGGAGGGACCAAGCTGACCGTC CTA	9
3N23 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG AGACTCTCCTGTGCAGTGTCTGGATTCACCTTCAGTAACTATGCCATGCACTGG GTCCGCCAGGCTCCAGGCAAGGGGCTGGACTGGGTGGCAGTTATATGGTATGAT GGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGA GACAATTCCAAGAACACGCTGTATCTGCAAGTGAACAGCCTGAGAGCCGAGGAC ACGGCTGTGTATTACTGTGCGAGGGGTGACTACGTTCTTGACTACTGGGGCCAG GGAACCCTGGTCACCGTCTCCTCA	10
3N23 light	GACATTGTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGA GTCACCATCAGTTGCCGGGCCAGTCAGAGCATTCCCAGCTATTTAAATTGGTAT CAACAGAAACCAGGGAAAGCCCCTAAGGTCCTGATCTATGCTACATCCACTTTG GAAGCTGGGGTCCCATCACGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACT	11

	CTCACCATCACCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAG AGTTACAATACGGGGATATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAA	
4J14 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTG AAGGTCTCCTGCAAGGCTTCTGGAGGCACTTCCAGCACTTATGCTATCAGCTGG GTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGCAGCATCCCTGTC TTTGCTACAGTAAACTACGCACAGAAGTTCCAGGGCAGACTCACGATTACCGCG GACGAATCCACGAGCACAGTTTACATGGAACTGAGCAGCCTGAGATCTGAGGAC ACGGCCGTTTATTTCTGTGCGAGCCCCTATTGTAGTAGTATGAACTGCTATACG ACCTTTTACTACTTTGACTTCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA	12
4J14 light	CAGGCTGTGGTGACTCAGCCTGCCTCCGTGTTTGGGTTTCCTGGACAGTCGATC ACCATCTCCTGCACTGGAACCAGCAGTGACTTTGGTACTTATAACTATGTCTCT TGGTACCAGCAACACCCAGGCCAAGCCCCCAAACTCATGATTTTTGATGTCAGT AATCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACG GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTTCTTATTACTGC AGCTCCTATACAAGCGGCAGCACTCTCTACGGCGGAGGGACCAAGCTGACCGTC CTG	13
4J21 heavy	CAGGTGCAGCTGGTGCAGTCTGGGTCTGAGTTGAAGAAGCCTGGGGCCTCAGTG AAGGTTTCCTGCAAGGCTTCTGGATACAGTTTCACTAGCTATTCTATCAACTGG GTGCGACAGGCCCCTGGACAAGGGCCTGAGTGGATGGGATGGATCGACACCAAC ACTGGGAACCCAACCTATGCCCAGGACTTCGCAGGACGGTTTGTCTTCTCCTTG GACACCTCTGTCACCACGGCATATCTGCAGATCAGCAGCCTAAAGGCTGGGGAC ACTGCCGTTTATTACTGTGCAACATATTATGTTGACCTTTGGGGGAGTTATCGC CAAGACTACTACGGTATGGACGTCTGGGGCCACGGGACCCTGGTCACCGTCTCC TCA	14
4J21 light	CAGTCTGTGGTGACTCAGCCACCCTCAGTGTCTGGGACCCCCGGGCAGGGGGTC ACCATCTCTTGTTCTGGAGGGAGCTCCAACATCGGGAGTAATCCTGTAAATTGG TACCAGATGGTCCCAGGAACGGCCCCCAAACTCCTCCTCTATACTAATAATCAG CGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCC TCCCTGGCCATCAATGGACTCCAGTCTGAGGATGAGGCTGATTATTACTGTGCA GTATGGGATGACAGCCTGAGTGGCCGTTGGGTGTTCggcggagggaccaagctg accgtccta	15
4N12 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTG AAGGTCTCCTGCAAGGTTTCCGGATACATCCTCAGTAAATTATCCGTGCACTGG GTGCGACAGGCTCCTGGAAAAGGACTTGAATGGATGGGAGGTTCTGAACGTGAA GATGGCGAAACAGTCTACGCACAGAAGTTCCAGGGCAGAATCAGCTTGACCGAG GACACATCTATAGAGACAGCCTACATGGAGCTGAGCAGCCTGAGTTCTGAGGAC ACGGCCGTGTATTATTGTGCAACAGGAGGCTTCTGGAGTATGATTGGGGGAAAT GGAGTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA	16
4N12 light	CAGGCTGTGGTGACTCAGTCTCCATCGTCCCTGCCTGCATCTGTAGGAGACAGG GTCACCATCACTTGCCGGGCAAGTCAGGACATTAGAAATAATTTAGGCTGGTAT CAGCAGAAACCAGGGAAAGCCCCTGAGCGCCTGATCTATGGAACCTCCAATTTG CAGAGTGGGGTCCCGTCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACT CTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAG CATAATAGTTACCCTCCCACGTTCGGCCGCGGGACCAAGGTGGAAATCAAA	17
5M16 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTG AGAGTTTCCTGCAAGGCATCTGGGTACACCTTCACCAGTTACTTTATGCACTGG GTGCGACAGGCCCCTGGACAAGGACTTGAGTGGATGGCGATAACTTATCCTGGT GGTGGTAGCCCATCCTACGCACCGCAGTTCCAGGGCAGACTCACCATGACCGAC GACACGTCCGCGACCACAGTCTACATGGACCTGAGTGACCTGACTTCTAAAGAC ACGGCCGTGTATTACTGTGCGAGAGGTGCCCACCGTTCCATTGGGACGACCCCC CTTGACTCGTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCAAGCTTCAAG GG	18
5O14 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGGACGCGTGGTCCAGGCTGGGAGGTCCCTG AGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTATGTATGGCGTCCACTGG GTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGAATGAT	19

	GGATCTAAAGAATACTATGGAGACTCCGTGAAGGGCCGATTCACCATCTCCAGA GACAATTCCAGGAACACGTTGTATCTGCAAATGAACAGCCTGAGAGTCGACGAC ACGGCAGTGTATTTTTGTGCGAGAGATGGAATTCCTGACCCTGAACGCGGTGAC TACGGGGGCTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA	
5O14 light	CAGACTGTGGTGACTCAGTTTCCATCCTCCCCGTTTGCATCTGTAGGAGACGGA GTCACCATCACTTGCCGGGCAAGGCAGAGCATTAGCAGTTATGTTAATTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATTTACGCTACATCCAGTTTG CAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATATGGGACAGATTTCACT CTCACCATCAGCGGTCTGCAACCTGAAGATTTTGCAACATACTACTGTCAACAG AGTTACAGTTTTCCTCGAACGTTCGGCCAAGGGACCAAGGTGGAAATCAAAC	20
8G18 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGCTCAGGTGAAGAAGCCTGGGTCCTCGGTG AAGGTCTCCTGCAAGCCCTCTGGAGGCACCTTCAACAACAATGGGATCAGTTGG GTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGCATCGTCCCGAAC TTTGGAACCCCAACCTATGGACAAGACTTCCAGGGCAGAGTCACGATCACCGCG GACGAATCTACGAGCACAGTCTTCTTGGAGCTGACCAGACTGAGATCTGACGAC ACGGCCGTTTATTTCTGTGCGCGAGGTCGCACGGCGGTGACTCCGATGCAATTG GGTTTACAGTTCTACTTTGACTTCTGGGGCCGGGGAACCCTGGTCACCGTCTCC TCA	21
8G18 light	cagactgtggtgactCAGGAGCCCTCACTGACTGTGTCCCCAGGAGGGACAGTC ACTCTCACCTGTTCTGCCAACAGTGGAGCAGTCACCAGTGATTACTATCCAAAC TGGTTCCAGCAGAAACCTGGACAAGCACCCAGGGCACTGATTTATAGTGCAAGC AACAAATTCTCCTGGACGCCTGCCCGGTTCTCAGGCTCCCTCCTTGGGGGCAAA GCTGCCCTGACACTGTCAGGTGCGCAGCCTGAGGACGAGGCTGAGTATTACTGC CTGGTCTACTCTGGTGATGGTGTGGTTTTCGGCGGAGGGACCAAGCTGACCGTC C	22
1I9 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCCGGGGCCTCAGTG AAGGTCTCCTGCAAGACTTCTGGATATACGTTCACCGACAACTCTGTACACTGG GTGCGACAGGCCCCTGGACAAGGGTTTGAGTGGATGGGACGGATCAACCCTAAC ACTGGTGTCTCAACTTCTGCCCAGAAGTTTCAGGGCAGGGTCACCATGACCAGG GACACGTCCATCAGCACAACCTACATGGAGCTGAGCAGTTTGAGATCTGACGAC ACGGCCGTCTATTACTGTGCGAGAGAGGAGAACGATAGTAGTGGGTATTACCTT TGGGGTCAGGGAACCCTGGTCACCGTCTCCTCA	23
1I9 light	CAGATTGTGGTGACTCAGTCTCCATCCTCCCTGTTTGCATCTGTAGGAGACAGA GTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCACCTATTTAAATTGGTAT CAGCAAAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTG GAGAGTGGGGTCCCATCAAGGTTCGGTGGCAGTAGATCTGGGACAGATTTCACT CTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAG AGTTACAGGACCCCGTGGACGTTCGGCCAAGGGACCAAGGTGGACATCAAA	24
1L1 heavy	CAGGTGCAGCTGGTGCAGTCTGGTCCTACGCTGGTGAAACCCACACAGACCCTC ACGCTGACCTGCACCTTCTCTGGGTTCTCACTCAGTATTAGTGGAGTGGGTGTG GGCTGGATCCGTCAGCCCCCAGGAAAGGCCCTGGAGTGGCTTGCACTCATTTAT TGGGATGATGATAAGCGCTACAGCCCATCTCTGAAGAGCAGGCTCACCATCACC AAGGACACCTCCGAAAACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTG GACACAGCCACATATTACTGTGCACACAGTATGACTAAAGGCGGGGCTATCTAT GGTCAGGCCTACTTTGAATACTGGGGCCAGGGAACCCTGGTC	25
1L1 light	CCATCTCCTGCACTGGAACCAGACAGTGACGTTGGTGGTTATAACTATGTCTCC TGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCATCATTTATGATGTCACT GATCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGCCTCCAAGTCTGCCAACACG GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGC AGCTCATATACAAGCAGCAGCACTCTGGTTTTCGGCGGAGGGACCAAGCTGACC GTCCTA	26
1M9 heavy	caggtccagctggtacagtctggggctgaggtgaagaagcctggGGCCTCAGTG AAGGTCTCCTGCAAGGTTTCCGGATACACCCTCACTGAATTATCCATGCACTGG GTGCGACAGGCTCCTGGAAAAGGCCTAGAGTGGATGGGAGGTTTTGAGCCTGAA	27

	GATGGTGAAACAATCTACGCACAGAAGTTCCAGGGCAGAGTCACCATGACCGAG GACACATCTAGAGACACAGCCTACATGGAGCTGAGTAGCCTGAGATCTGAGGAC ACGGCCGTCTATTACTGTACAACAGATCAGGTCTACTATCGTTCGGGGAGTTAT TCTGGATATGTTGACTACTGGGGCCAGGGAACCCTGGTC	
1O5 heavy	caggtccagctggtgcagtctggggctgaggtgaagaagcctgggtCCTCAGTG AAGGTCTCCTGCAAGGCTTCTGGACGCACCTTCAGCAGCTATGTTATCAGCTGG GTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTCTG TTTGGTACAGCAAACTACGCACAGAAATTCCAGGGCAGAGTCACGATTACCGCG GACGAATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGACGAC ACGGCCGTCTATTACTGTGCGAGGGGCGCCCAGCTATATTACAATGATGGTAGT GGTTACATTTTTGACTACTGGGGCCAGGGAGCCCTGGTC	28
1O6 heavy	CAGGTGCAGCTGGTGCAGTCTGGGCCTGAGGTGAAGAAGCCTGGGACCTCAGTG AAGGTCTCCTGCAAGGCTTCTGGATTCAGCTTTATTAGCTCTGCTGTGCAGTGG GTGCGACAGGCTCGTGGACAACGCCTTGAGTGGATAGGATGGATCGTCGTTGCC AGTGCTAACACAAACTACGCACAGAAGTTCCGGGAAAGAGTCACCATTACTAGG GACATGTCCACAAACACAGCCTATATGGAACTGACCAGCCTGAGATCCGAGGAC ACGGCCGTTTATTACTGTGCGGCAGAGCACCGGTCCCCTTGTAGTGGTGGTGAT AGCTGCTACAGTCTCTACTACGGTATGGACGTCTGGGGCCAAGGGACCCTGGTC ACCGTCTCCTCA	29
2A2 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTTCCGCCTGGGGGGTCCCTG AGACTGTCCTGTACAGCCTCTGGATTCACCGTTAGTAACTATGGCATGAGCTGG GTCCGCCAGACTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTAGTACTAGT AGTGGTAGAACATTCTACGCAGACTCCGTGGAGGGCCGGTTCACCATCTCCGGA GACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGTCGAAGAC ACGGCCGTATATTACTGTGCGAAAGGCCCGTTCGGGGGCGACTTTGACTACTGG GGCCAGGGAACCCTGGTCACCGTCTCCTCA	30
2A2 light	CAGGCTGTGGTGACTCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGA GCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTGCCATCTACTTAGCCTGGTAT CAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGG GCCACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACT CTCACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAG CGTGGCAACTGGCAGTACACTTTTGGCCAGGGGACCAAACTGGAGATCAAA	31
2C2 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCCTGGTACAGCCTGGCAGGTCCCTG ACACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGTTTATGCCATGCACTGG GTCCGGCAAGCTCCAGGGAAGGGCTTGGAGTGGGTCGCAGGTATTAGTTGGAAT AGTGGTAGCGTAGGCTATGCGGACTCTATGAAGGGCCGATTCACCATCTCCAGA GACAACGCCAAGAACTCCCTGTATCTGCAAATTAACAGTCTGAGAGCTGAGGAC ACGGCCTTATATTACTGTGCAAAAGCATTCTGGTTCGGGGAGTTATCGGGTTAC GGTATGGACGTCTGGGGCCAAGGGACCCTGGTCACCGTCTCCTCA	32
2C2 light	CAGGCTGTGGTGACTCAGCCTCCCTCCGCGTCCGGGTTTCCTGGACAGTCAGTC ACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTAGTTATAACTATGTCTCC TGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATAATTTATGCGGTCACT AGGCGGCCCTCAGGGGTCCCTGAGCGCTTCTCTGGCTCCAAGTCTGGCAACACG GCCTCCCTGACCGTCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGC ACCTCATATGCAGGCAACAACAAGGATGTCTTCGGAACTGGGACCAAGGTCACC GTCCTA	33

2D12 heavy	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTG AAGGTCTCCTGCAAGGCTTCTGGTTACAGCTTTAACATCTATGGTATCAGCTGG GTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTAC AATGGTAACACAAACTATGCACAGAAACTCCAGGGCAGAGTCACCATGACCACA GACACATCCACGAGCACAGCCTACATGGAACTGAGGAGCCTGAGATCTGACGAC ACGGCCGTGTATTACTGTGCGAGACCACTTTGGGGGGAATTTTACTATGATATC TGGGGCCAAGGGACCCTGGTCACCGTCTCCTCA	34
2D12 light	CAGGCTGTGGTGACTCAGTCTCCAGGCACCCTGTCCTTGTCTCCAGGGGAAAGA GCCACCCTCTCTTGCAGGGCCAGTCAGAGTGTTAGCAGCGGGTACTCAGCCTGG TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAAA AGGGCCGCTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTC ACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CTGTTTGCTACCTCACCTCCGCCCTTCGGCCAAGGGACACGACTGGAGATTAAA	35
3A2 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG AGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTAATTATGTTATGGAGTGG GTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCATATGAT GGAAGCAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGA GACAATTCCAAGAACACGTTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGAC ACGGCTGTGTATTACTGTGCGAGATCAGAGTGGGAGTCTTCCTATGGTTCGGGG AATTATTATACAGATTACTTCTACTACTACGCTATGGACGTCTGGGGCCCAGGG ACCCTGGTCACCGTCTCCTCA	36
3A2 light	CAGGCTGTGGTGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCG GCCTCCATCTCCTGCAGGTCTAATCAGAGCCTCCTGCGTGGTATTAGATACAAC TATTTGGATTGGTACCTGCAGAAACCAGGGCAGTCTCCACAGCTCCTGATCTAT TTGGGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGGCAGTGGATCA GCCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTT TATTACTGCATGCAAGCTCTACAAACTCCTACCACCTTCGGCCAAGGGACACGA CTGGAGATTAAA	37
3B4 heavy	CAGGTGCAGCTGGAGGAGTCTGGTCCTACGCTGGTGAAACCCACACAGACCCTC ACGCTGACCTGTTCCTTCTCTGGGTTCTCACTCACCACTACTGGAGTGACTGTG GGCTGGATCCGTCAGCCCCCAGGAAAGGCCTTGGAGTGGCTTGCACTCATTTAT TGGGATGATGATAAGCGCTACAGCCCATCTCTGAAGAGCAGGCTCACCATCACC AAGGACACCTCCAAAAACCAGGTGGTCCTTACCATGACCAACATGGACCCTGTG GACACTGCCACATATTACTGTGCGCACTCCACCGGCTACTATGATAGTAGTGGC TATCGAGGGGCCCTTGATGCTTTTGCTGTCTGGGGCCAAGGGACCCTGGTCACC GTCTCCTCA	38
3B4 light	CAGATTGTGGTGACTCAGTTTCCAGACTCCCCGGCTGTGTCTTTGGGCGAGAGG GCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACCACTCCAACAATAAA AACTACTTAGCTTGGTACCAGCAGAAACCAGGACAGCCTCCTAACCTGCTCATT TACTGGGCATCTGCCCGACAATCCGGGGTCCCTGACCGATTCAGTGGCAGCGGG TCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGATGTGGCA GTTTATTACTGTCAGCAATATTATAGTACTCCGTACACTTTTGGCCAGGGGACC AAGCTGGAGATCAAA	39
3E23 heavy	CAGGTGCAGCTGGTGCAGTCGGGCCCAGGACTGGTGAAGCCTTCGGACACCCTG TCCCTCACCTGCAGTGTCTCAAGTGACGCCCTCCGCAGCAGGAGTTATTACTGG GGCTGGGTCCGCCAGCCCCCCGGGAAGGGATTGGAGTGGATTGGGACTGTCTCT TATAGTGGGGGCACCTACTACAACCCGTCCCTCCAGAGTCGAGTCACCGTGTCG GTGGACACGTCCAAGAACCACTTCTCCCTGAGGTTGAACTCTGTGACCGCCGCA GACGCGGCTGTTTATTACTGTGCGAGATCTTATTTCTATGATGGCAGTGGTTAC TACTACCTGAGCTACTTTGACTCCTGGGGCCAGGGAACCCTGGTCACCGTCTCC TCA	40
3E23 light	CAGGCTGTGGTGACTCAGGAGCCCTCACTGACTGTGTCCCCAGGAGGGACAGTC ACTCTCACCTGTGCTTCCAGCACTGGAGCAGTCACCAGTGGTCACTATCCAAAC TGGTTCCAGCAGAAACCTGGACAACCACCCAGGGCCCTGATTTATAGCACAGAC	41

	AACAAGCACTCCTGGACCCCTGCCCGGTTCTCAGGCTCCCTCCTAGGGGTCAAG GCTGCCCTGACACTGTCAGATGTACAGCCTGAGGACGAGGCTGACTATTACTGC CTGCTCCATTTTGGTGGTGTCGTGGTCTTCGGCGGAGGGACCAAGCTGACCGTC CTA	
3H5 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG AGACTCTCCTGTTCAACGTCTGGATTCACCTTCAGGATGTATGGCATGCACTGG GTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCCGTTATTTTTAACGAT GGAGTTAAGAAATATTATGGAGACGCCGTGAAGGGCCGATTCACCGTCTCCAGA GACAATTCCAGGAACACCCTGTATCTGGAAATGAAAAGCCTGAGAGTCGACGAC ACGGCTGCCTACTACTGTGCGAGAGACGGGATTCCTGACCCCGAACGCGGTGAC TACGGGGGCTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA	42
3H5 light	CAGACTGTGGTGACTCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACACA GTCACCATCACTTGCCGGGCAAGTCAGAGCATTACCAGTTATTTAAACTGGTAT CAGCAGAAACCAGGAAAAGCCCCAAAGCTCCTCATCTATGCTACATCCAGTTTG CAAAGTGGGCTCCCCTCAAGGTTCAGTGGCAGTGGCTATGGGACAGAATTCACT CTCACCATCAGTGGTCTGCAACCTGAAGATTTTGCAACATACTACTGTCAACAG AGTTACAGTTTTCCTCGAACGTTCGGCCAAGGGACCAAGGTGGAAATGGATA	43
3I21 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTG AGACTCTCCTGTGCAACCTCTGGATTCATCTTTGATGATTATGCCATGTACTGG GTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAAT AGTGGAAACATAGCCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGA GACAACGCCAAGAACTCCCTGTATTTGGAAATGAACAGTCTGAGAGCTGAGGAC ACGGCCTTGTATTACTGTGTAAAAGATCTTTACGGGTACGATATTTTGACTGGT AATGGATATGATTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA	44
3I21 light	CAGGCTGTGGTGACTCAGTCTTCACTCTCCCTGCCCGTCACCCCTGGAGAGCCG GCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCAAAGTAATGGATACAAC TATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTGATCTAT TTGGGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGGCAGTGGATCA GGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTT TATTACTGCATGCAAGCTCTACAAACTCCTCCGACGTTCGGCCAAGGGACCAAG GTGGAAATCAAAA	45
3K11 heavy	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTG AAGGTCCCCTGCAAGGCTTCTGGAGACACCCTCAGTTACTACGGAATCACTTGG GTGCGACGGGCCCCTGGACAAGGGCTTGAGTGGATGGGACAGATCATCCCTTTC TTTGCTACAACAATCTCCGCACAGAAGTTCCAGGGCAGACTCACCATGACCGCG GAAGAATCCACGAGCACTGGCTACATGGAGCGCACATTTTACATGGACTTGAGT AGCCTTAGACCTGAGGACACGGCCGTATACTACTGTGCGGGGGGCTACTATGGT TCGGGGAGTTCGGGCGACTACGGTTTGGACGTCTGGGGCCAAGGGACCCTGGTC ACCGTCTCCTCA	46
3K11 light	CAGGCTGTGGTGACTCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAGGGTC ACCATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCAGGTTATGATGTAAAC TGGTACCAGCAGCTTCCAGGAACAGCCCCCAAACTCCTCATCTATGGTAACAAC AATCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCA GCCTCCCTGGCCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGC CAGTCCTATGACAGCAGCCTGAGTGGTTCGGGAGTCTTCGGAACTGGGACCGAG GTCACCGTCCTA	47
4B8 heavy	CAGGTGCAGCTGGTGCAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTG TCCCTGACGTGCGCTGTTTCTGGTGACTCCATCGGCAGTAGAAGTTTCTACTGG GGCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGGATTGGAAGTATCTAT TATAATGGGACCACCTACTACAAGCCGTCCCTCAAGAGTCGAGTCACCATATCC CTAGACACGTCCAAGAACCAGTTCTCCCTGAGGCTGAGCTCTCTGACCGCCACA GACACGGGTGTCTATTACTGTGCGCGGGCGCCAACCTACTGTAGTCCTTCCAGC TGCGCAGTTCACTGGTACTTCAATCTCTGGGGCCGTGGCACCCTGGTCACCGTC TCCTCA	48

4B10 heavy	CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGCTGAAGAAGCCTGGGGCCTCAGTG AAGGTCTCCTGCAAGGCTTCTGGTTACATATTTACCAAATATGGTATCAGTTGG CTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGGTGGGATGGATCAGCGCTTAC AATGAAAACACAAACTATGCAGAGAAGTTCCAGGGCAGAGTCACCTTGACCACA GATGCATCCACGAGCACGGCCTACATGGAGCTGAGGAACCTGAGATCTGACGAC ACGGCCGTATACTTCTGTGCGAGAGAAGTCTGGTTCGCGGAGTATATTTACTGG GGCCAGGGAACCCTGGTCACCGTCTCCTCA	49
8E22 light	CAGGCTGTGGTGACTCAGGAGCCCTCACTGACTGTGTCCCCAGGAGGGACAGTC ACTCTCACCTGTTCTGCCAACAGTGGAGCAGTCACCAGTGATTACTATCCAAAC TGGTTCCAGCAGAAACCTGGACAAGCACCCAGGGCACTGATTTATAGTGCAAGC AACAAATTCTCCTGGACGCCTGCCCGGTTCTCAGGCTCCCTCCTTGGGGGCAAA GCTGCCCTGACACTGTCAGGTGCGCAGCCTGAGGACGAGGCTGAGTATTACTGC CTGGTCTACTCTGGTGATGGTGTGGTTTTC GGCGGAGGGACCAAGCTGACCGTCCTAA	50
9A11 light	CAGTCTGTGGTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATC ACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGCTTATAACTATGTCTCC TGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCGTGATTTATGATGTCGCT AATCGGCCCTCAGGGATTTCTGACCGCTTCTCTGGCTCCAAGTCTGGCAACACG GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGC GGCTCATATACCAGCGACGTCTCGCCGGTTTTCAGCGGGGGGACCAAGCTGACC GTCCTCA	51
9D14 heavy	CAGGTGCAGCTGGTGCAGTCTGGGTCTGAGTTGAAGAAGCCTGGGGCCTCAGTG AAGCTTTCCTGCAAGGCTTCTGGATACACCTTCACAAGTCATCCTATGAATTGG GTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAACACCAAG ACTGGGAACCTAACTTATGCCCAGGGCTTCACAGGACGGTTTGTCTTCTCCTTG GACACCTCTGTCAGGACGGCGTATCTGCAGATCAGCGGCCTAAAGGCTGAGGAC ACTGCCATTTATTACTGTGCGAGAGATGAGTATAGTGGCTACGATTCGGTAGGG GTGTTCCGTGGTTCTTTTGACGACTTCTACGGTATGGACGTCTGGGGCCAAGGG ACCCTGGTCACCGTCTCCTCA	52

TABLE 2 – PROTEIN SEQUENCES FOR ANTIBODY VARIABLE REGIONS

Clone	Variable Sequence	SEQ ID NO:
1H12 heavy	QVQLVQSGAEVKKPGASVKVSCKASGYSFTSYGISWVRQAPGQGLEWMG WISTYKGYTQYAQNFQGRVTITTDTPATTVYMELRSLRSDDTAVYYCAR VLSETGYFYYYYYGMDVWGQGTLVTVSS	53
1H12 light	QAVVTQPPSVSGAPGQRVTISCTGSSSNIGADYNVHWYQLLPGTAPKLL IYGNTNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLS ASVFGGGTKLTVL	54
2B4 heavy	QVQLVQSGSELKKPGASVKVSCKASGYSFTSYSINWVRQAPGQGPEWMG WIDTNTGNPTYAQDFAGRFVFSLDTSVTTAYLQISSLKAGDTAVYYCAT YYVDLWGSYRQDYYGMDVWGH	55
2B4 light	QSVLTQPPSASGTPGQRVTISCSGGSSNIGSNPVNWYQMVPGTAPKLLL YTNNQRPSGVPDRFSGSKSGTSASLAINGLQSEDEADYYCAVWDDSLSG RWVFGGGTKVTVL	56
2H1 heavy	QVQLVQSGAEVKKPGASVRVSCKASGYTFTSYGISWVRQAPGQGLEWMG WISTYNGDTNYAQKFQGRVTLTTETSTSTAYMELRRLRSDDTAVYYCAR DFEFPGDCSGGSCYSRFIYQHNDMDVWGHGTLVTVSSAS	57
2H1 light	QAVVTQPPSVSAAPGQKVTISCSGSSSNIGNHYVSWYQHLPGTAPKLLI YDNYKRPSVIPDRFSASKSGASATLGIIGLQTGDEADYYCGTWDSSLSA VVFGGGTKLTVL	58

3E23 heavy	QVQLVQSGPGLVKPSDTLSLTCSVSSDALRSRSYYWGWVRQPPGKGLEW IGTVSYSGGTYYNPSLQSRVTVSVDTSKNHFSLRLNSVTAADAAVYYCA RSYFYDGSGYYYLSYFDSWGQGTLVTVSS	59
3E23 light	QAVVTQEPSLTVSPGGTVTLTCASSTGAVTSGHYPNWFQQKPGQPPRAL IYSTDNKHSWTPARFSGSLLGVKAALTLSDVQPEDEADYYCLLHFGGVV VFGGGTKLTVL	60
3N23 heavy	QVQLVQSGGGVVQPGRSLRLSCAVSGFTFSNYAMHWVRQAPGKGLDWVA VIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQVNSLRAEDTAVYYCAR GDYVLDYWGQGTLVTVSS	61
3N23 light	DIVMTQSPSSLSASVGDRVTISCRASQSIPSYLNWYQQKPGKAPKVLIY ATSTLEAGVPSRFSGSGSGTDFTLTITSLQPEDFATYYCQQSYNTGIFT FGPGTKVDIK	62
4J14 heavy	QVQLVQSGAEVKKPGSSVKVSCKASGGTSSTYAISWVRQAPGQGLEWMG GSIPVFATVNYAQKFQGRLTITADESTSTVYMELSSLRSEDTAVYFCAS PYCSSMNCYTTFYYFDFWGQGTLVTVSS	63
4J14 light	QAVVTQPASVFGFPGQSITISCTGTSSDFGTYNYVSWYQQHPGQAPKLM IFDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEASYYCSSYTSGST LYGGGTKLTVL	64
4J21 heavy	QVQLVQSGSELKKPGASVKVSCKASGYSFTSYSINWVRQAPGQGPEWMG WIDTNTGNPTYAQDFAGRFVFSLDTSVTTAYLQISSLKAGDTAVYYCAT YYVDLWGSYRQDYYGMDVWGHGTLVTVSS	65
4J21 light	QSVVTQPPSVSGTPGQGVTISCSGGSSNIGSNPVNWYQMVPGTAPKLLL YTNNQRPSGVPDRFSGSKSGTSASLAINGLQSEDEADYYCAVWDDSLSG RWVFGGGTKLTVL	66
4N12 heavy	QVQLVQSGAEVKKPGASVKVSCKVSGYILSKLSVHWVRQAPGKGLEWMG GSEREDGETVYAQKFQGRISLTEDTSIETAYMELSSLSSEDTAVYYCAT GGFWSMIGGNGVDYWGQGTLVTVSS	67
4N12 light	QAVVTQSPSSLPASVGDRVTITCRASQDIRNNLGWYQQKPGKAPERLIY GTSNLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSYPPTF GRGTKVEIK	68
5M16 heavy	QVQLVQSGAEVKKPGASVRVSCKASGYTFTSYFMHWVRQAPGQGLEWMA ITYPGGGSPSYAPQFQGRLTMTDDTSATTVYMDLSDLTSKDTAVYYCAR GAHRSIGTTPLDSWGQGTLVTVSSASFK	69
5O14 heavy	QVQLVQSGGRVVQAGRSLRLSCAASGFTFSMYGVHWVRQAPGKGLEWVA VIWNDGSKEYYGDSVKGRFTISRDNSRNTLYLQMNSLRVDDTAVYFCAR DGIPDPERGDYGGLDYWGQGTLVTVSS	70
5O14 light	QTVVTQFPSSPFASVGDGVTITCRARQSISSYVNWYQQKPGKAPKLLIY ATSSLQSGVPSRFSGSGYGTDFTLTISGLQPEDFATYYCQQSYSFPRTF GQGTKVEIK	71
8G18 heavy	QVQLVQSGAQVKKPGSSVKVSCKPSGGTFNNNGISWVRQAPGQGLEWMG GIVPNFGTPTYGQDFQGRVTITADESTSTVFLELTRLRSDDTAVYFCAR GRTAVTPMQLGLQFYFDFWGRGTLVTVSS	72
8G18 light	QTVVTQEPSLTVSPGGTVTLTCSANSGAVTSDYYPNWFQQKPGQAPRAL IYSASNKFSWTPARFSGSLLGGKAALTLSGAQPEDEAEYYCLVYSGDGV VFGGGTKLTV	73
1I9 heavy	QVQLVQSGAEVKKPGASVKVSCKTSGYTFTDNSVHWVRQAPGQGFEWMG RINPNTGVSTSAQKFQGRVTMTRDTSISTTYMELSSLRSDDTAVYYCAR EENDSSGYYLWGQGTLVTVSS	74
1I9 light	QIVVTQSPSSLFASVGDRVTITCRASQSISTYLNWYQQKPGKAPKLLIY AASSLESGVPSRFGGSRSGTDFTLTISSLQPEDFATYYCQQSYRTPWTF	75

	GQGTKVDIK	
1L1 heavy	QVQLVQSGP.TLVKPTQTLTLTCTFSGFSLSISGVGVGWIRQPPGKALE WLALIYWDDDKRYSPSLKSRLTITKDTSENQVVLTMTNMDPVDTATYYC AHSMTKGGAIYGQAYFEYWGQGTLV	76
1L1 light	PSPALEPDSDVGGYNYVSWYQQHPGKAPKLIIYDVTDRPSGVSNRFSAS KSANTASLTISGLQAEDEADYYCSSYTSSST	77
1M9 heavy	QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMG GFEPEDGETIYAQKFQGRVTMTEDTSRDTAYMELSSLRSEDTAVYYCTT DQVYYRSGSYSGYVDYWGQGTLV	78
1O5 heavy	QVQLVQSGAEVKKPGSSVKVSCKASGRTFSSYVISWVRQAPGQGLEWMG GIIPLFGTANYAQKFQGRVTITADESTSTAYMELSSLRSDDTAVYYCAR GAQLYYNDGSGYIF DYWGQGALV	79
1O6 heavy	QVQLVQSGPEVKKPGTSVKVSCKASGFSFISSAVQWVRQARGQRLEWIG WIVVASANTNYAQKFRERVTITRDMSTNTAYMELTSLRSEDTAVYYCAA EHRSPCSGGDSCYSLYYGMDVWGQGTLVTVSS	80
2A2 heavy	QVQLVQSGGGLVPPGGSLRLSCTASGFTVSNYGMSWVRQTPGKGLEWVS TISTSSGRTFYADSVEGRFTISGDNSKNTLYLQMNSLRVEDTAVYYCAK GPFGGDFDYWGQGTLVTVSS	81
2A2 light	QAVVTQSPATLSLSPGERATLSCRASQSVAIYLAWYQQKPGQAPRLLIY DASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRGNWQYTF GQGTKLEIK	82
2C2 heavy	QVQLVQSGGGLVQPGRSLTLSCAASGFTFDVYAMHWVRQAPGKGLEWVA GISWNSGSVGYADSMKGRFTISRDNAKNSLYLQINSLRAEDTALYYCAK AFWFGELSGYGMDVWGQGTLVTVSS	83
2C2 light	QAVVTQPPS.ASGFPGQSVTISCTGTSSDVGSYNYVSWYQQHPGKAPKL IIYAVTRRPSGVPERFSGSKSGNTASLTVSGLQAEDEADYYCTSYAGNN KDVFGTGTKVTVL	84
2D12 heavy	QVQLVQSGAEVKKPGASVKVSCKASGYSFNIYGISWVRQAPGQGLEWMG WISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR PLWGEFYYDIWGQGTLVTVSS	85
2D12 light	QAVVTQSPGTLSLSPGERATLSCRASQSVSSGYSAWYQQKPGQAPRLLI YGASKRAAGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLFATSPPP FGQGTRLEIK	86
3A2 heavy	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSNYVMEWVRQAPGKGLEWVA VISYDGSNKYYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA RSEWESSYGSGNYYTDYFYYYAMDVWGPGTLVTVSS	87
3A2 light	QAVVTQSPLSLPVTPGEPASISCRSNQSLLRGIRYNYLDWYLQKPGQSP QLLIYLGSNRASGVPDRFSGSGSATDFTLKISRVEAEDVGVYYCMQALQ TPTTFGQGTRLEIK	88
3B4 heavy	QVQLEESGPTLVKPTQTLTLTCSFSGFSLTTTGVTVGWIRQPPGKALEW LALIYWDDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYYCA HSTGYYDSSGYRGALDAFAVWGQGTLVTVSS	89
3B4 light	QIVVTQFPDSPAVSLGERATINCKSSQSVLYHSNNKNYLAWYQQKPGQP PNLLIYWASARQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYY STPYTFGQGTKLEIK	90
3E23 heavy	QVQLVQSGPGLVKPSDTLSLTCSVSSDALRSRSYYWGWVRQPPGKGLEW IGTVSYSGGTYYNPSLQSRVTVSVDTSKNHFSLRLNSVTAADAAVYYCA RSYFYDGSGYYYLSYFDSWGQGTLVTVSS	91
3E23	QAVVTQEPS.LTVSPGGTVTLTCASSTGAVTSGHYPNWFQQKPGQPPRA	92

light	LIYSTDNKHSWTPARFSGSLLGVKAALTLSDVQPEDEADYYCLLHFGGV VVFGGGTKLTVL	
3H5 heavy	QVQLVQSGGGVVQPGRSLRLSCSTSGFTFRMYGMHWVRQAPGKGLEWVA VIFNDGVKKYYGDAVKGRFTVSRDNSRNTLYLEMKSLRVDDTAAYYCAR DGIPDPERGDYGGLDYWGQGTLVTVSS	93
3H5 light	QTVVTQSPSSLSASVGDTVTITCRASQSITSYLNWYQQKPGKAPKLLIY ATSSLQSGLPSRFSGSGYGTEFTLTISGLQPEDFATYYCQQSYSFPRTF GQGTKVEMD	94
3I21 heavy	QVQLVQSGGGLVQPGRSLRLSCATSGFIFDDYAMYWVRQAPGKGLEWVS GISWNSGNIAYADSVKGRFTISRDNAKNSLYLEMNSLRAEDTALYYCVK DLYGYDILTGNGYDYWGQGTLVTVSS	95
3I21 light	QAVVTQSSLSLPVTPGEPASISCRSSQSLLQSNGYNYLDWYLQKPGQSP QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ TPPTFGQGTKVEIK	96
3K11 heavy	QVQLVQSGAEVKKPGSSVKVPCKASGDTLSYYGITWVRRAPGQGLEWMG QIIPFFATTISAQKFQGRLTMTAEESTSTGYMERTFYMDLSSLRPEDTA VYYCAGGYYGSGSSGDYGLDVWGQGTLVTVSS	97
3K11 light	QAVVTQPPS.VSGAPGQRVTISCTGSSSNIGAGYDVNWYQQLPGTAPKL LIYGNNNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSL SGSGVFGTGTEVTVL	98
4B8 heavy	QVQLVQSGPGLVKPSETLSLTCAVSGDSIGSRSFYWGWIRQPPGKGLEW IGSIYYNGTTYYKPSLKSRVTISLDTSKNQFSLRLSSLTATDTGVYYCA RAPTYCSPSSCAVHWYFNLWGRGTLVTVSS	99
4B10 heavy	QVQLVQSGAELKKPGASVKVSCKASGYIFTKYGISWLRQAPGQGLEWVG WISAYNENTNYAEKFQGRVTLTTDASTSTAYMELRNLRSDDTAVYFCAR EVWFAEYIYWGQGTLVTVSS	100
9A11 light	QSVVTQPASVSGSPGQSITISCTGTSSDVGAYNYVSWYQQHPGKAPKLV IYDVANRPSGISDRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSDVS PVFSGGTKLTVL	101
9D14 heavy	QVQLVQSGSELKKPGASVKLSCKASGYTFTSHPMNWVRQAPGQGLEWMG WINTKTGNLTYAQGFTGRFVFSLDTSVRTAYLQISGLKAEDTAIYYCAR DEYSGYDSVGVFRGSFDDFYGMDVWGQGTLVTVSS	102

TABLE 3 – CDR HEAVY CHAIN SEQUENCES

Antibody	**CDRH1 (SEQ ID NO:)**	**CDRH2 (SEQID NO:)**	**CDRH3 (SEQ ID NO:)**
1H12	GYSFTSYG (103)	ISTYKGYT (104)	ARVLSETGYFYYYYYGMDV (105)
2B4	GYSFTSYS (106)	IDTNTGNP (107)	ATYYVDLWGSYRQDYYGMDV (108)
2H1	GYTFTSYG (109)	ISTYNGDT (110)	ARDFEFPGDCSGGSCYSRFIYQHNDMDV (111)
3E23	SDALRSRSYY (112)	VSYSGGT (113)	ARSYFYDGSGYYYLSYFDS (114)

3N23	GFTFSNYA (115)	IWYDGSNK (116)	ARGDYVLDY (117)
4J14	GGTSSTYA (118)	SIPVFATV (119)	ASPYCSSMNCYTTFYYFDF (120)
4J21	GYSFTSYS (121)	IDTNTGNP (122)	ATYYVDLWGSYRQDYYGMDV (123)
4N12	GYILSKLS (124)	SEREDGET (125)	ATGGFWSMIGGNGVDY (126)
5M16	GYTFTSYF (127)	TYPGGGSP (128)	ARGAHRSIGTTPLDS (129)
5O14	GFTFSMYG (130)	IWNDGSKE (131)	ARDGIPDPERGDYGGLDY (132)
8G18	GGTFNNNG (133)	IVPNFGTP (134)	ARGRTAVTPMQLGLQFYFDF (135)
1I9	GYTFTDNS (136)	INPNTGVS (137)	AREENDSSGYYL (138)
1L1	GFSLSISGVG (139)	IYWDDDK (140)	AHSMTKGGAIYGQAYFEY (141)
1M9	GYTLTELS (142)	FEPEDGET (143)	TTDQVYYRSGSYSGYVDY (144)
1O5	GRTFSSYV (145)	IIPLFGTA (146)	ARGAQLYYNDGSGYIFDY (147)
1O6	GFSFISSA (148)	IVVASANT (149)	AAEHRSPCSGGDSCYSLYYGMDV (150)
2A2	GFTVSNYG (151)	ISTSSGRT (152)	AKGPFGGDFDY (153)
2C2	GFTFDVYA (154)	ISWNSGSV (155)	AKAFWFGELSGYGMDV (156)
2D12	GYSFNIYG (157)	ISAYNGNT (158)	ARPLWGEFYYDI (159)
3A2	GFTFSNYV (160)	ISYDGSNK (161)	ARSEWESSYGSGNYYTDYFYYYAMDV (162)
3B4	GFSLTTTGVT (163)	IYWDDDK (164)	AHSTGYYDSSGYRGALDAFAV (165)
3E23	SDALRSRSYY (166)	VSYSGGT (167)	ARSYFYDGSGYYYLSYFDS (168)
3H5	GFTFRMYG (169)	IFNDGVKK (170)	ARDGIPDPERGDYGGLDY (171)
3I21	GFIFDDYA (172)	ISWNSGNI (173)	VKDLYGYDILTGNGYDY (174)
3K11	GDTLSYYG (175)	IIPFFATT (176)	TAVYYCAGGYYGSGSSGDYGLDV (177)

4B8	GDSIGSRSFY (178)	IYYNGTT (179)	ARAPTYCSPSSCAVHWYFNL (180)
4B10	GYIFTKYG (181)	ISAYNENT (182)	AREVWFAEYIY (183)
9D14	GYTFTSHP (184)	INTKTGNL (185)	ARDEYSGYDSVGVFRGSFDDFYGMDV (186)

TABLE 4 – CDR LIGHT CHAIN SEQUENCES

Antibody	CDRL1 (SEQ ID NO:)	CDRL2 (SEQID NO:)	CDRL3 (SEQ ID NO:)
1H12	SSNIGADYN (187)	GNT (188)	QSYDSSLSASV (189)
2B4	SSNIGSNP (190)	TNN (191)	AVWDDSLSGRWV (192)
2H1	SSNIGNHY (193)	DNY (194)	GTWDSSLSAVV (195)
3E23	TGAVTSGHY (196)	STD (197)	LLHFGGVVV (198)
3N23	QSIPSY (199)	ATS (200)	QQSYNTGIFT (201)
4J14	SSDFGTYNY (202)	DVS (203)	SSYTSGSTLYGGG (204)
4J21	SSNIGSNP (205)	TNN (206)	AVWDDSLSGRWV (207)
4N12	QDIRNN (208)	GTS (209)	LQHNSYPPT (210)
5O14	QSISSY (211)	ATS (212)	QQSYSFPRT (213)
8G18	SGAVTSDYY (214)	SAS (215)	LVYSGDGVV (216)
1I9	QSISTY (217)	AAS (218)	QQSYRTPWT (219)
1L1	DSDVGGYNY (220)	DVT (221)	SSYTSSSTLV (222)
2A2	QSVAIY (223)	DAS (224)	QQRGNWQYT (225)
2C2	SSDVGSYNY (226)	AVT (227)	TSYAGNNKDV (228)
2D12	QSVSSGY (229)	GAS (230)	QLFATSPPP (231)
3A2	QSLLRGIRYNY (232)	LGS (233)	MQALQTPTT (234)
3B4	QSVLYHSNNKNY (235)	WAS (236)	QQYYSTPYT (237)
3E23	TGAVTSGHY (238)	STD (239)	LLHFGGVVV (240)
3H5	QSITSY (241)	ATS (242)	QQSYSFPRT (243)
3I21	QSLLQSNGYNY (244)	LGS (245)	MQALQTPPT (246)
3K11	SSNIGAGYD (247)	GNN (248)	QSYDSSLSGSGV (249)
9A11	SSDVGAYNY (250)	DVA (251)	GSYTSDVSPV (252)

TABLE 5 - CHARACTERISTICS OF CHIKUNGUNYA VIRUS-SPECIFIC HUMAN MONOCLONAL ANTIBODIES

mAb[1]	IgG sub-class[2]	λ/κ light chain[2]	ELISA binding to E2 ectodomain (10 μg/mL)[3]	Neutralization against CHIKV VRP (strain SL15649)[4] EC_{50} in ng/mL[5] [95% confidence interval]
2H1	IgG2	λ	++	8 [6 - 10]
4N12	IgG2	κ	-	8 [7 - 10]
2B4	IgG1	λ	++	14 [11 - 17]
4J21	IgG1	λ	++	5 [4 - 6]
5M16	IgG1	κ	+++	5 [4 - 6]
9D14	IgG1	λ	+++	6 [5 - 7]
1H12	IgG1	λ	+++	17 [14 - 20]
8E22	IgG1	λ	++	17 [14 - 19]
8G18	IgG1	λ	++	17 [14 - 19]
10N24	IgG1	κ	-	21 [17 - 26]
8I4	IgG1	κ	+++	8 [5 - 14]
3N23	IgG1	κ	-	25 [21 - 30]
5O14	IgG1	κ	+++	38 [30 - 47]
4J14	IgG1	λ	++	23 [20 - 26]
3E23	IgG2	λ	-	11 [9 - 13]
1L1	IgG1	λ	+/-	18 [15 - 22]
3B4	IgG3	κ	-	>
4B8	IgG1	λ	+++	0.6 [0.4 - 0.8]
4G20	IgG1	λ	-	95 [60 - 160]
1O5	IgG1	λ	-	138 [110 - 170]
1O6	IgG3	λ	-	5,200 [4,100 – 6,600]
2L5	NT	NT	-	4,600 [2,400 – 9,500]
3A2	IgG1	κ	+++	1,300 [830 – 1,900]
5F19	IgG1	λ	+++	>
1M9	IgG1	κ	-	>
1I9	IgG1	κ	-	>
4B10	IgG1	κ	-	>
2C2	IgG1	λ	-	>
2D12	IgG1	κ	-	>
5N23	IgG1	λ	+++	>
murine CHK-152	IgG2c	κ	-	3 [2 - 4]

[1]Order of antibodies reflects the level of potency degree and breadth of the antibodies in neutralization assays against clinical CHIKV isolates of diverse genotypes.

[2]Immunoglobulin isotype, subtype, and light chain use were determined by ELISA. NT indicates not tested due to poor growth of B cell line.

[3] (-) denotes no detectable binding [OD <0.1]; (+/-) denotes weak binding [OD 0.31-0.499]; (++) denotes moderate binding [OD 0.5-0.99]; (+++) denotes strong binding [OD >1.0].
[4]Values shown represent combined data from two or more independent experiments.
[5]Concentration (ng/mL) at which 50% of virus was neutralized (EC_{50}). (>) indicates EC_{50} value is greater than the highest mAb concentration tested (10 μg/ml). N.D. = Not Done.

TABLE 6 - MAJOR ANTIGENIC SITES OF CHIKUNGUNYA VIRUS-SPECIFIC HUMAN MONOCLONAL ANTIBODIES

mAb[1]	Competition binding group for purified E2 protein[2]	Mutagenesis mapping	
		E2 Domain[3]	E2 residues for which reduced binding was noted when altered to alanine
2H1	Low binding	E2-DA	R80, T116
4N12	NT	Arch	D250
2B4	Low binding	NoReduct ##	-
4J21	Low binding	NoReduct	-
5M16	2	Arch	G253
9D14	2	NoReduct	-
1H12	1/2	DA/B, Arch	T58, D59, D60, R68, D71, I74, D77, T191, N193, K234
8E22	Low binding	DA, Arch	H62, W64, R68, H99, D117, I255
8G18	Low binding	DA	H62, W64, D117
10N24	NT	DA,B	W64, D71, R80, T116, D117, I121, N187, I190
8I4	NSF Ab	DB, Arch	M171, Q184, I190, N193, V197, R198, Y199, G209, L210, K215, K234, V242, I255
3N23	NT	DA, Arch	D60, R68, G98, H170, M171, K233, K234
5O14	2	NoReduct	-
4J14	Low binding	DA/B	D63, W64, T65, R80, I121, A162, N193
3E23	NT	DA	W64
1L1	Low binding	Arch	G253
3B4	NT	DB	V192, Q195
4B8	2	NoReduct	-
4G20	NT	DB	D174, R198, Y199, K215
1O5	NT	DA	W64, T65
1O6	2	DA	R80
2L5	NT	NoReduct	-
3A2	3	DB	I190, R198, Y199, G209, L210, T212
5F19	4	DA	H18

1M9	NT	DA, Arch	R36, H62, R80, Q146, E165, E166, N231, D250, H256
1I9	NT	E2	Inconclusive
4B10	NT	NoReduct	-
2C2	NT	NoReduct	Inconclusive
2D12	NT	E2	Inconclusive
5N23	1	DA, Arch	E24, D117, I121
murine CHK-152	NT	E2-DA, E2-DB	D59, W235, A11, M74, G194, N193, T212, H232[4]

[1]Order of antibodies reflects the level of potency degree and breadth of the antibodies in neutralization assays against clinical CHIKV isolates of diverse genotypes.

[2]Values shown represent combined data from two independent experiments. *Low binding* indicates incomplete mAb binding to E2 on biosensor for assessing competition. NT indicates not tested since Ab did not bind E2 ectodomain in ELISA; *NSF Ab* indicates insufficient supply of mAb.

[3]*NotReact* indicates that the mAb did not react against the wild-type envelope proteins and could not be tested in this system. *NoReduct* indicates the mAb did bind to the wild-type E proteins, but no reduction was noted reproducibly for any mutant. DA indicates domain A; DB indicates domain B; Arch indicates either arch 1, arch 2, or both.

[4]Residues identified by contacts with mAb in a previous cryo-EM reconstruction.

TABLE 7 - *IN VITRO* NEUTRALIZING POTENCY AND BREADTH OF CHIKUNGUNYA VIRUS-SPECIFIC HUMAN MONOCLONAL ANTIBODIES

mAb[1]	Neutralization against CHKV against indicated genotype and strain* EC_{50}, ng/mL[2] (95% confidence interval)			
	West African genotype	ECSA genotype	Asian genotype	
	NI 64 IbH 35 strain	LR2006 OPY1 (LR) strain	RSUI strain	2014 Caribbean 99659 strain
2H1	3.7 (3.3-4.3)	5.6 (4.9-6.3)	5.9 (5.3-6.7)	5.5 (4.7-6.5)
4N12	2.5 (2.0-3.1)	4.0 (3.3-5.0)	6.5 (5.7-7.3)	7.3 (5.9-9.2)
2B4	3.2 (2.8-3.7)	5.6 (4.6-6.7)	6.5 (5.6-7.7)	7.0 (6.0-8.2)
4J21	5.2 (4.3-6.4)	7.4 (6.6-8.3)	7.7 (7.0-8.6)	7.2 (5.3-9.8)
5M16	6. 0 (5.5-6.6)	5.9 (5.0-6.8)	8.4 (6.7-10.4)	11.7 (9.7-14.1)
9D14	2.1 (1.6-2.7)	2.9 (2.3-3.7)	6.3 (4.7-8.4)	86.0 (31.5-235)
1H12	3.0 (2.5-3.5)	7.5 (6.7-8.4)	11.7 (9.3-14.8)	11.6 (8.2-16.2)
8E22	8.2 (7.0-9.7)	7.2 (6.4-8.3)	42.5 (30.8-58.5)	138.9 (64.7-298)
8G18	4.7 (4.1-5.3)	7.3 (6.3-8.4)	34.9 (24.9-48.9)	52.4 (24.1-114)
10N24	7.9 (6.9-9.0)	9.5 (8.2-11.0)	15.9 (13.2-19.2)	23.6 (18.3-30.5)
8I4	6.9 (3.8-12.3)	6.2 (4.5-8.4)	153 (78-299)	>
3N23	6.0 (5.0-7.2)	10.1 (8.9-11.5)	14.1 (11.6-17.1)	8.7 (7.0-10.9)
5O14	6.7 (5.5-8.3)	12.1 (10.9-13.5)	17.3 (14.2-21.1)	6.2 (5.3-7.2)
4J14	12.9 (11.2-15.0)	17.7 (16.1-19.4)	23.1 (20-27)	23.0 (18.5-28.4)
3E23	19.4 (15.2-25.0)	18.7 (16.3-21.5)	36.0 (30.3-42.9)	38.0 (30.3-47.5)
1L1	18.6 (15.5-22.4)	24.2 (21.3-27.5)	34.3 (29-40.7)	N.D.
3B4	18.7 (10.7-32.8)	29.6 (18.7-46.8)	271 (144-511)	N.D.
4B8	22.8 (12.4-41.8)	28.1 (19.8-39.9)	234 (142-386)	N.D.
4G20	22.3 (17.3-29.0)	34.9 (28.2-43.8)	131.4 (88.5-195)	N.D.
1O5	30.1 (22.6-35.3)	37.6 (32.6-43.4)	48.9 (37.8-63.2)	N.D.
1O6	61.7 (50.8-74.8)	57.5 (48.8-68.1)	N.D.	N.D.
2L5	1,076 (748-1,548)	2,361 (1,460-3,819)	5,632 (3,904-8,128)	N.D.
3A2	1,566 (1,111-2,207)	1,396 (952-2,046)	>	N.D.
5F19	>	9,064 (2,911-28,249)	>	N.D.
1M9	>	>	6,187 (2,795-13,709)	N.D.
1I9	>	>	>	N.D.
4B10	>	>	>	N.D.
2C2	>	>	>	N.D.
2D12	>	>	>	N.D.
5N23	>	>	>	N.D.
murine CHK-152				

[1]Order of antibodies reflects the level of potency degree and breadth of the antibodies in neutralization assays against clinical CHIKV isolates of diverse genotypes.

[2]Concentration (ng/mL) at which 50% of virus was neutralized (EC_{50}). (>) indicates EC_{50} value is greater than the highest mAb concentration tested (10 μg/ml). N.D. = Not Done.

* * * * * * * * * * * * * * * * *

All of the compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this disclosure have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the disclosure. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the disclosure as defined by the appended claims.

VII. REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

"Antibodies: A Laboratory Manual," Cold Spring Harbor Press, Cold Spring Harbor, NY, 1988.

Abbondanzo *et al.*, *Am. J. Pediatr. Hematol. Oncol.*, 12(4), 480-489, 1990.

Allred *et al.*, *Arch. Surg.*, 125(1), 107-113, 1990.

Atherton *et al., Biol. of Reproduction*, 32, 155-171, 1985.

Austin *et al.,* PLoS Pathog 8, e1002930, 2012.

Brehin, *et al.,* Virology 371:185-195, 2008.

Brown *et al.*, *J. Immunol. Meth.*, 12;130(1), :111-121, 1990.

Campbell, *In*: *Monoclonal Antibody Technology, Laboratory Techniques in Biochemistry and Molecular Biology*, Vol. 13, Burden and Von Knippenberg, Eds. pp. 75-83, Amsterdam, Elsevier, 1984.

Capaldi *et al.*, *Biochem. Biophys. Res. Comm.*, 74(2):425-433, 1977.

CDC, Chikungunya in the Americas. (Atlanta, GA: US Department of Health and Human Services). world-wide-web at cdc.gov/chikungunya/geo/americas.html, 2014.

CDC, Chikungunya virus (Atlanta, GA: US Department of Health and Human Services). world-wide-web at cdc.gov/media/releases/2013/p1218-chikungunyas.html, 2013.

Christian *et al.,* Proc Natl Acad Sci U S A, 110:18662-18667, 2013.

Chu *et al.,* Deciphering the protective role of adaptive immunity to CHIKV/IRES a novel candidate vaccine against Chikungunya in the A129 mouse model. Vaccine 31:3353-3360, 2013.

Couderc *et al.,* J. Infect. Dis. 200, 516-523, 2009.

De Jager *et al.*, *Semin. Nucl. Med.* 23(2), 165-179, 1993.

Dholakia *et al., J. Biol. Chem.*, 264, 20638-20642, 1989.

Doolittle and Ben-Zeev, *Methods Mol. Biol.*, 109, :215-237, 1999.

Edwards & Brown, J. Gen. Virol. 67 (Pt 2), 377-380, 1986.

Edwards *et al.,* J. Gen. Virol. 67 (Pt 2), 377-380, 1986.

Fong *et al.,* J. Virol. 88:14364-14379, 2014.

Fric *et al.*, J. Infect. Dis. 207:319-322, 2013.

Gefter *et al.*, *Somatic Cell Genet.*, 3:231-236, 1977.

Goh *et al.,* Clin. Immunol. 149:487-497, 2013.

Gulbis and Galand, *Hum. Pathol.* 24(12), 1271-1285, 1993.

Guo *et al.*, *Sci. Transl. Med.* 3:99 ra85, 2001.

Hallengard, *et al.*, J. Virol. 88:13333-13343, 2014.

Hawman *et al.,* J. Virol. 87, 13878-13888, 2013.

Hong *et al.,* J. Virol. 87:12471-12480, 2013.

Kam *et al.*, EMBO Mol. Med. 4, 330-343, 2012b.

Kam *et al.*, J. Virol. 86, 13005-13015, 2012a.

Kam *et al.,* PLoS One 9, e95647, 2014.

Khatoon *et al., Ann. of Neurology*, 26, 210-219, 1989.

Kielian *et al.,* Viruses 2:796-825, 2010.

King *et al., J. Biol. Chem.*, 269, 10210-10218, 1989.

Kohler and Milstein, *Eur. J. Immunol.*, 6, 511-519, 1976.

Kohler and Milstein, *Nature*, 256, 495-497, 1975.

Krause *et al.,* J. Immunol. 187:3704-3711, 2011b.

Krause *et al.,* J. Virol. 84:3127-3130, 2010.

Krause *et al.,* J. Virol. 85:10905-10908, 2011a.

Krause *et al.*, J. Virol. 86:6334-6340, 2012.

Kyte and Doolittle, *J. Mol. Biol.,* 157(1):105-132, 1982.

Lanciotti & Valadere, Emerg Infect Dis 20, 2014.

Lee *et al.*, PLoS Pathog. 7:e1002390, 2011.

Levitt *et al.,* Vaccine 4, 157-162, 1986.

Lum *et al.,* J. Immunol. 190:6295-6302, 2013.

Mainou *et al.,* MBio 4, 2013.

Masrinoul *et al.*, Virology 464-465, 111-117, 2014.

Messer *et al.,* Proc. Natl. Acad. Sci. U. S. A. 111:1939-1944, 2014.

Morrison *et al.,* Am J Pathol, 178:32-40, 2011.

Nakamura *et al.*, *In*: *Enzyme Immunoassays: Heterogeneous and Homogeneous Systems*, Chapter 27, 1987.

O'Shannessy *et al., J. Immun. Meth.*, 99, 153-161, 1987.

Paes *et al.,* J. Am. Chem. Soc., 131:6952-6954, 2009.

Pal *et al.,* J. Virol. 88:8213-8226, 2014.

Pal *et al.,* PLoS Pathog 9, e1003312, 2013.

Persic *et al.*, *Gene* 187:1, 1997

Potter and Haley, *Meth. Enzymol.*, 91, 613-633, 1983.

Remington's Pharmaceutical Sciences, 15th Ed., 3:624-652, 1990.

R.C. Team, R Foundation for Statistical Computing, Vienna, Austria, 2014.

Schilte *et al.,* PLoS Negl. Trop. Dis. 7:e2137, 2013.

Selvarajah *et al.,* PLoS Negl. Trop. Dis. 7:e2423, 2013.

Sissoko *et al.,* PLoS Negl. Trop. Dis. 3:e389, 2009.

Smith *et al.,* J. Virol. 86, 2665-2675, 2012.

Smith *et al.,* J. Virol. 88, 12233-12241, 2014.

Smith *et al.,* J. Virol., 86:2665-2675, 2012.

Smith et al., MBio 4, e00873-00813, 2013a.

Smith *et al.,*, J. Infect. Dis. 207, 1898-1908, 2013b.

Staples *et al.,* Clin. Infect. Dis., 49, 942-948, 2009.

Sun *et al.,* Elife, 2:e00435, 2013.

Sun *et al., J. Steroid Biochem.*, 26(1):83-92, 1987.

Sun *et al.,* J. Virol., 88:2035-2046, 2014.

Tang *et al., J. Biol. Chem.,* 271:28324-28330, 1996.

Thornburg *et al.,* J. Clin. Invest., 123:4405-4409, 2013.

U.S. Patent 3,817,837

U.S. Patent 3,850,752

U.S. Patent 3,939,350

U.S. Patent 3,996,345

U.S. Patent 4,196,265

U.S. Patent 4,275,149

U.S. Patent 4,277,437

U.S. Patent 4,366,241

U.S. Patent 4,472,509

U.S. Patent 4,554,101

U.S. Patent 4,680,338

U.S. Patent 4,816,567

U.S. Patent 4,867,973

U.S. Patent 4,938,948

U.S. Patent 5,021,236

U.S. Patent 5,141,648

U.S. Patent 5,196,066

U.S. Patent 5,563,250

U.S. Patent 5,565,332

U.S. Patent 5,856,456

U.S. Patent 5,880,270

Vander Veen *et al.,* Anim Health Res Rev, 13:1-9, 2012.

Voss *et al.,* Nature, 468:709-712, 2010.

Voss *et al.,* Nature, 468:709-712, 2010.

Warter *et al.,* J. Immunol., 186:3258-3264, 2011.

Warter *et al.,* J. Immunol., 186:3258-3264, 2011.

Wawrzynczak & Thorpe, In: *Immunoconjugates, Antibody Conuugates In Radioimaging And Therapy Of Cancer*, Vogel (Ed.), NY, Oxford University Press, 28, 1987.

Yu *et al.,* Nature 455:532-536, 2008.

WHAT IS CLAIMED IS:

1. A method of detecting a Chikungunya virus infection in a subject comprising:

   (a) contacting a sample from said subject with an antibody or antibody fragment having clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively; and

   (b) detecting Chikungunya virus glycoprotein E2 in said sample by binding of said antibody or antibody fragment to E2 in said sample.

2. The method of claim 1, wherein said sample is a body fluid.

3. The method of claims 1-2, wherein said sample is blood, sputum, tears, saliva, mucous or serum, urine or feces.

4. The method of claims 1-3, wherein detection comprises ELISA, RIA or Western blot.

5. The method of claims 1-4, further comprising performing steps (a) and (b) a second time and determining a change in the E2 levels as compared to the first assay.

6. The method of claims 1-5, wherein the antibody or antibody fragment is encoded by clone-paired variable sequences as set forth in Table 1.

7. The method of claims 1-5, wherein said antibody or antibody fragment is encoded by light and heavy chain variable sequences having 70%, 80%, or 90% identity to clone-paired variable sequences as set forth in Table 1.

8. The method of claims 1-5, wherein said antibody or antibody fragment is encoded by light and heavy chain variable sequences having 95% identity to clone-paired sequences as set forth in Table 1.

9. The method of claims 1-5, wherein said antibody or antibody fragment comprises light and heavy chain variable sequences according to clone-paired sequences from Table 2.

10. The method of claims 1-5, wherein said antibody or antibody fragment comprises light and heavy chain variable sequences having 70%, 80% or 90% identity to clone-paired sequences from Table 2.

11. The method of claims 1-5, wherein said antibody or antibody fragment comprises light and heavy chain variable sequences having 95% identity to clone-paired sequences from Table 2.

12. The method of claims 1-11, wherein the antibody fragment is a recombinant ScFv (single chain fragment variable) antibody, Fab fragment, $F(ab')_2$ fragment, or Fv fragment.

13. A method of treating a subject infected with Chikungunya Virus, or reducing the likelihood of infection of a subject at risk of contracting Chikungunya virus, comprising delivering to said subject an antibody or antibody fragment having clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively.

14. The method of claim 13, the antibody or antibody fragment is encoded by clone-paired light and heavy chain variable sequences as set forth in Table 1.

15. The method of claim 13-14, the antibody or antibody fragment is encoded by clone-paired light and heavy chain variable sequences having 95% identify to as set forth in Table 1.

16. The method of claim 13-14, wherein said antibody or antibody fragment is encoded by light and heavy chain variable sequences having 70%, 80%, or 90% identity to clone-paired sequences from Table 1.

17. The method of claim 13, wherein said antibody or antibody fragment comprises light and heavy chain variable sequences according to clone-paired sequences from Table 2.

18. The method of claim 13, wherein said antibody or antibody fragment comprises light and heavy chain variable sequences having 70%, 80% or 90% identity to clone-paired sequences from Table 2.

19. The method of claim 13, encoded by light and heavy chain variable sequences having 95% identity to clone-paired sequences from Table 2.

20. The method of claims 13-19, wherein the antibody fragment is a recombinant ScFv (single chain fragment variable) antibody, Fab fragment, $F(ab')_2$ fragment, or Fv fragment.

21. The method of claims 13-20, wherein said antibody is an IgG.

22. The method of claims 13-19, wherein said antibody is a chimeric antibody.

23. The method of claim 13-22, wherein said antibody or antibody fragment is administered prior to infection.

24. The method of claim 13-22, wherein said antibody or antibody fragment is administered after infection.

25. The method of claim 13-24, wherein delivering comprises antibody or antibody fragment administration, or genetic delivery with an RNA or DNA sequence or vector encoding the antibody or antibody fragment.

26. A monoclonal antibody, wherein the antibody or antibody fragment is characterized by clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively.

27. The monoclonal antibody of claim 26, wherein said antibody or antibody fragment is encoded by light and heavy chain variable sequences according to clone-paired sequences from Table 1.

28. The monoclonal antibody of claim 26, wherein said antibody or antibody fragment is encoded by light and heavy chain variable sequences having at least 70%, 80%, or 90% identity to clone-paired sequences from Table 1.

29. The monoclonal antibody of claim 26, wherein said antibody or antibody fragment is encoded by light and heavy chain variable sequences having at least 95% identity to clone-paired sequences from Table 1.

30. The monoclonal antibody of claim 26, wherein said antibody or antibody fragment comprises light and heavy chain variable sequences according to clone-paired sequences from Table 2.

31. The monoclonal antibody of claim 26, wherein said antibody or antibody fragment comprises light and heavy chain variable sequences having 95% identity to clone-paired sequences from Table 2.

32. The monoclonal antibody of claims 26-31, wherein the antibody fragment is a recombinant ScFv (single chain fragment variable) antibody, Fab fragment, $F(ab')_2$ fragment, or Fv fragment.

33. The monoclonal antibody of claims 26-31, wherein said antibody is a chimeric antibody, or is bispecific antibody that targets a Chikungunya virus antigen other than glycoprotein.

34. The monoclonal antibody of claim 26-33, wherein said antibody is an IgG.

35. The monoclonal antibody of claim 26-34, wherein said antibody or antibody fragment further comprises a cell penetrating peptide and/or is an intrabody.

36. A hybridoma or engineered cell encoding an antibody or antibody fragment wherein the antibody or antibody fragment is characterized by clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively.

37. The hybridoma or engineered cell of claim 36, wherein said antibody or antibody fragment is encoded by light and heavy chain variable sequences according to clone-paired sequences from Table 1.

38. The hybridoma or engineered cell of claim 36, wherein said antibody or antibody fragment is encoded by light and heavy chain variable sequences having at least 70%, 80%, or 90% identity to clone-paired variable sequences from Table 1.

39. The hybridoma or engineered cell of claim 36, wherein said antibody or antibody fragment is encoded by light and heavy chain variable sequences having 95% identity to clone-paired variable sequences from Table 1.

40. The hybridoma or engineered cell of claim 36, wherein said antibody or antibody fragment comprises light and heavy chain variable sequences according to clone-paired sequences from Table 2.

41. The hybridoma or engineered cell of claim 36, wherein said antibody or antibody fragment is encoded by light and heavy chain variable sequences having at least 70%, 80%, or 90% identity to clone-paired variable sequences from Table 2.

42. The hybridoma or engineered cell of claim 36, wherein said antibody or antibody fragment comprises light and heavy chain variable sequences having 95% identity to clone-paired sequences from Table 2.

43. The hybridoma or engineered cell of claims 36-42, wherein the antibody fragment is a recombinant ScFv (single chain fragment variable) antibody, Fab fragment, $F(ab')_2$ fragment, or Fv fragment.

44. The hybridoma or engineered cell of claim 36-43, wherein said antibody is a chimeric antibody.

45. The hybridoma or engineered cell of claim 36-43, wherein said antibody is an IgG.

46. The hybridoma or engineered cell of claim 36-45, wherein said antibody or antibody fragment further comprises a cell penetrating peptide and/or is an intrabody.

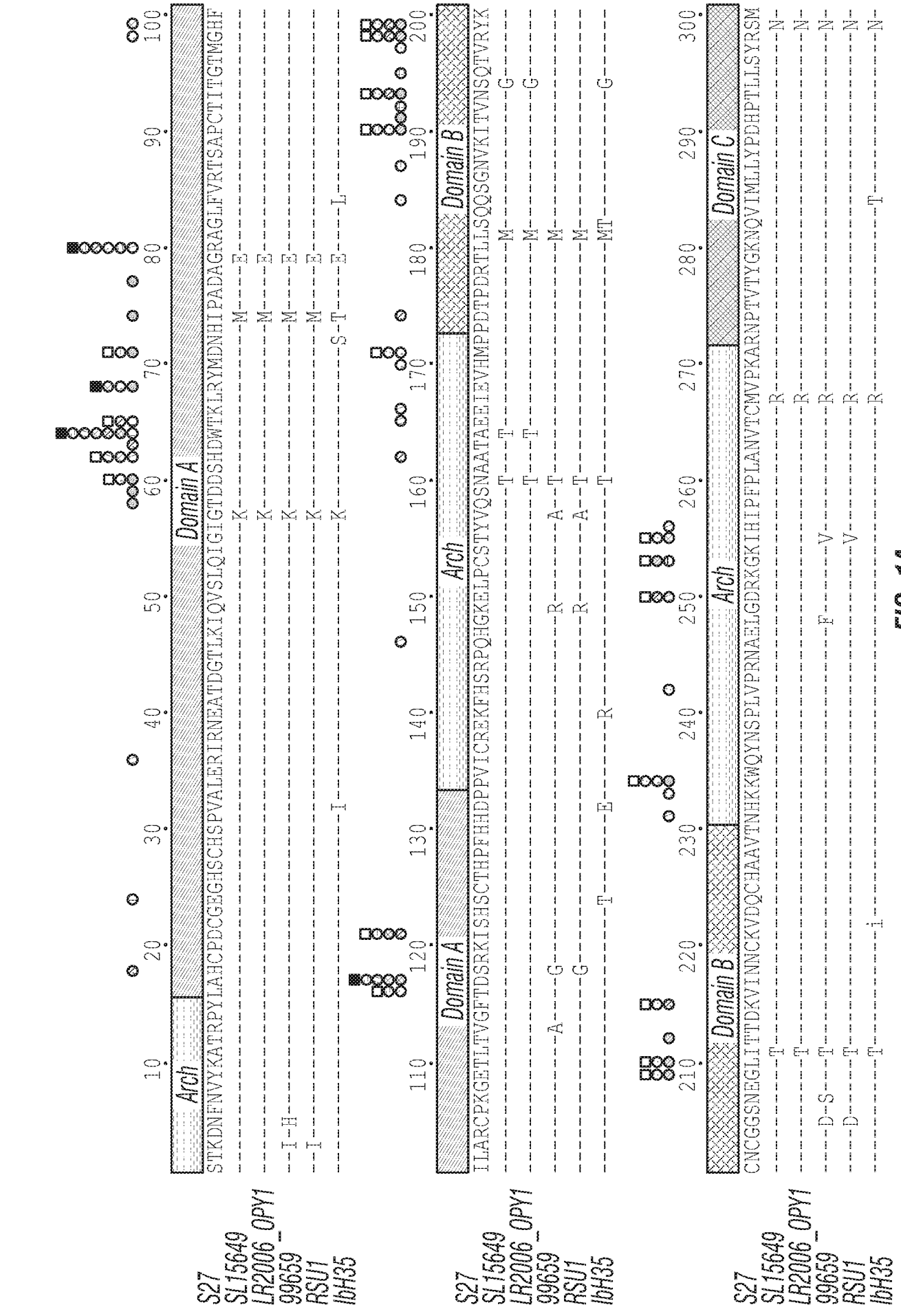

Arch
Domain A
Domain A
Arch
Domain B
Domain B
Arch
Domain C
S27
SL15649
LR2006_OPY1
99659_
RSU1
IbH35

FIG. 1A

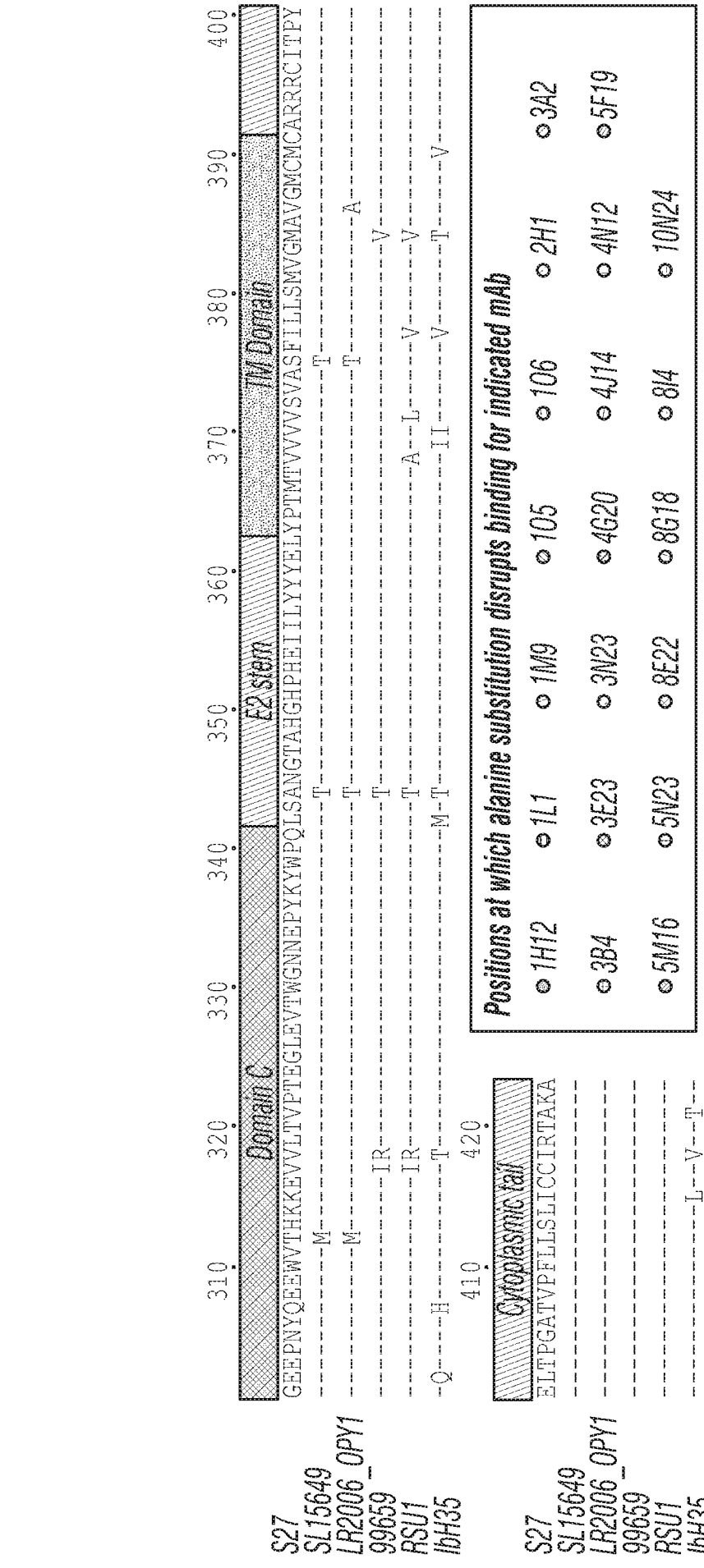

310
320
330
340
350
360
370
380
390
400
Domain C
E2 stem
TM Domain
S27 GEEPNYQEEWVTHKKEVVLTVPTEGLEVTWGNNEPYKYWPQLSANGTAHGHPHEIILYYYELYPTMTVVVVSVASFILLSMVGMAVGMCMCARRRCITPY
SL15649 ----------M----------T----------T----------
LR2006_OPY1 ----------M----------T----------T----------A----------
99659_ ----------IR----------T----------V----------
RSU1 ----------IR----------T----------A--L----V----V----------
IbH35 -Q----H----------T----------M-T----------II----V----T----V----------
Cytoplasmic tail
S27 ELTPGATVPFLLSLICCIRTAKA
SL15649 ----------
LR2006_OPY1 ----------
99659_ ----------
RSU1 ----------
IbH35 ----------L--V--T--
Positions at which alanine substitution disrupts binding for indicated mAb
1H12
1L1
1M9
1O5
1O6
2H1
3A2
3B4
3E23
3N23
4G20
4J14
4N12
5F19
5M16
5N23
8E22
8G18
8I4
10N24

FIG. 1A
(Cont'd)

FIG. 1C

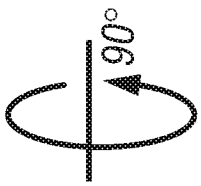


FIG. 1B

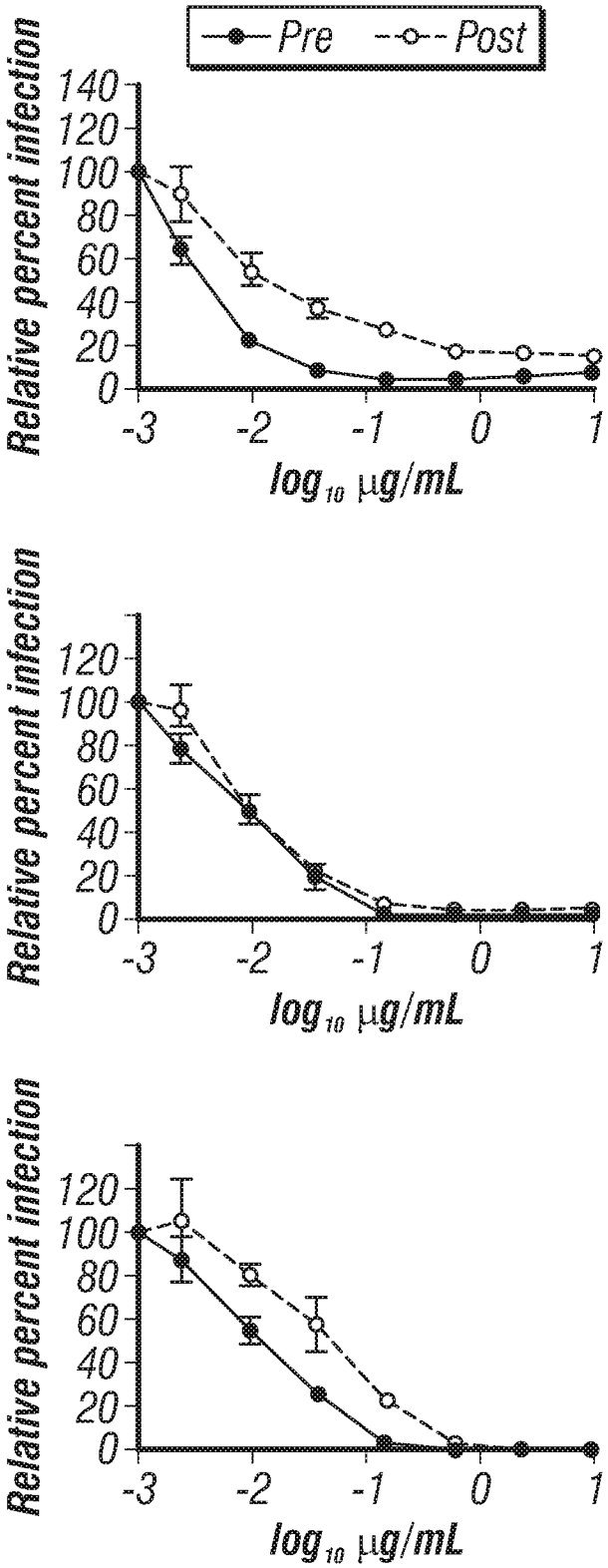

Pre
Post
Relative percent infection
140
120
100
80
60
40
20
0
-3
-2
-1
0
1
log10 µg/mL

FIG. 2A

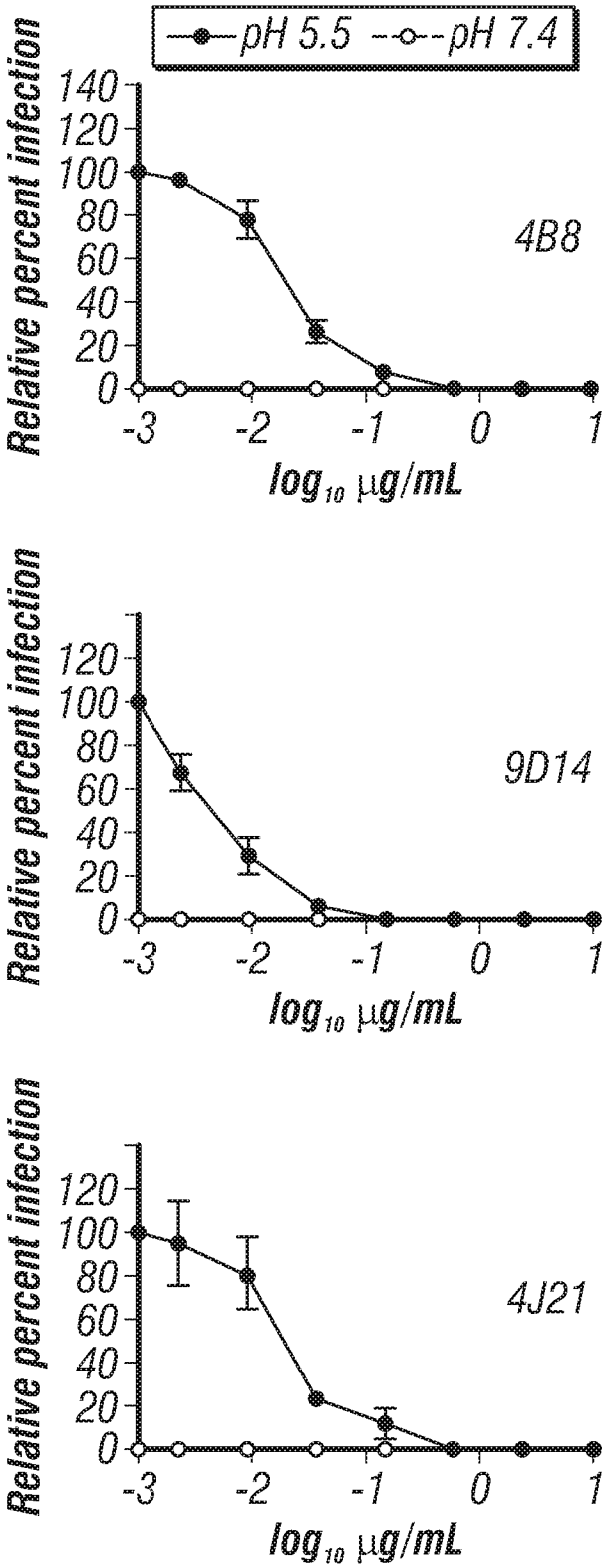
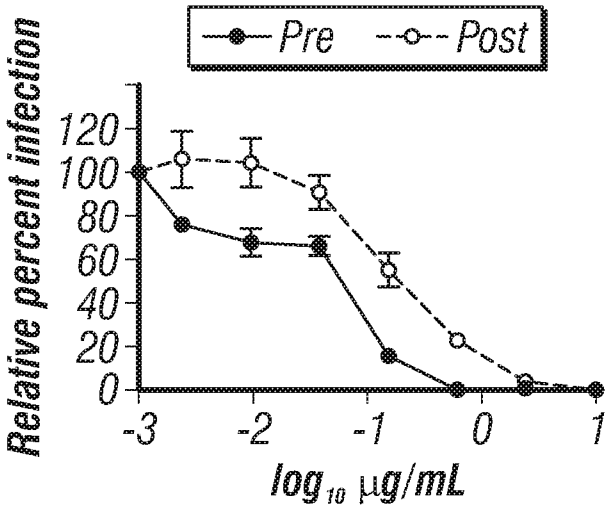
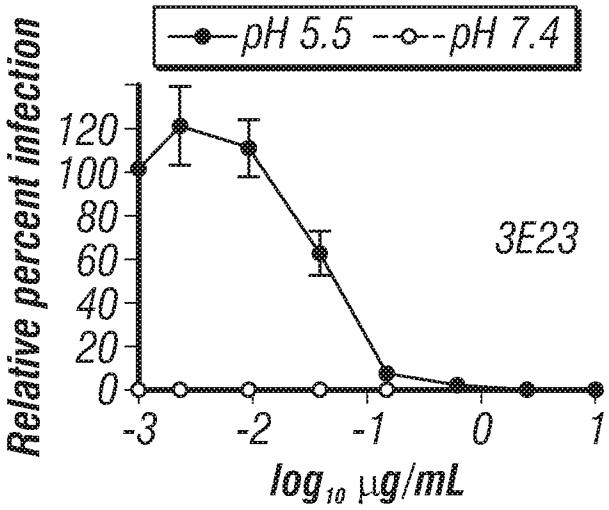
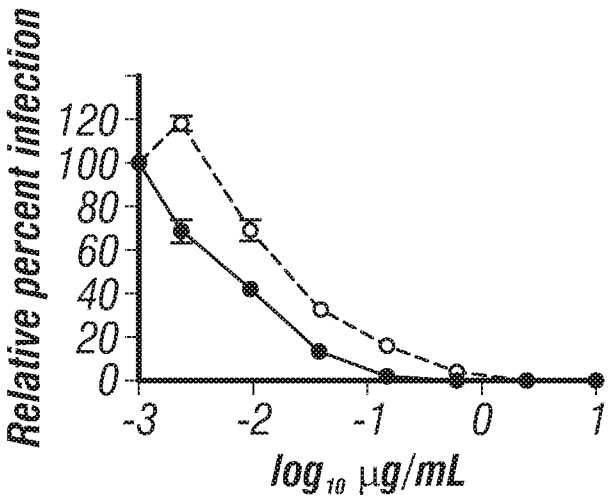
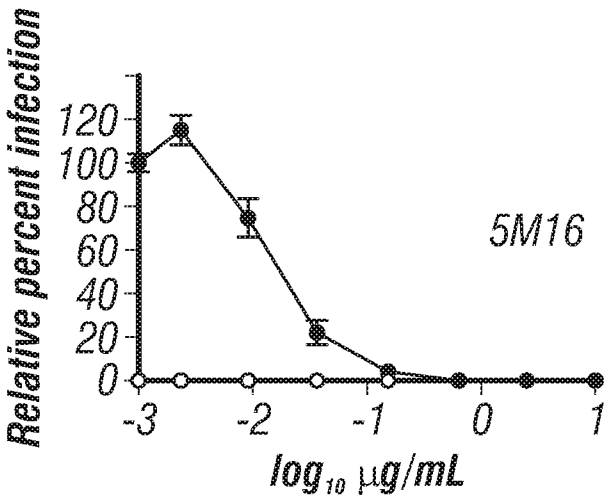

pH 5.5
pH 7.4
Relative percent infection
4B8
9D14
4J21
log10 µg/mL

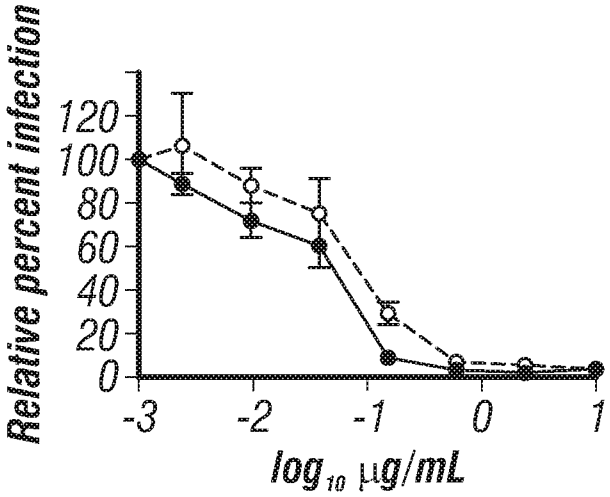
FIG. 2B











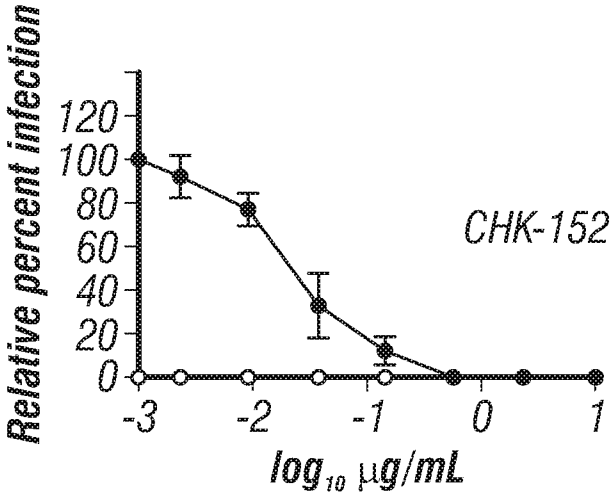


FIG. 2A
(Cont'd)

FIG. 2B
(Cont'd)

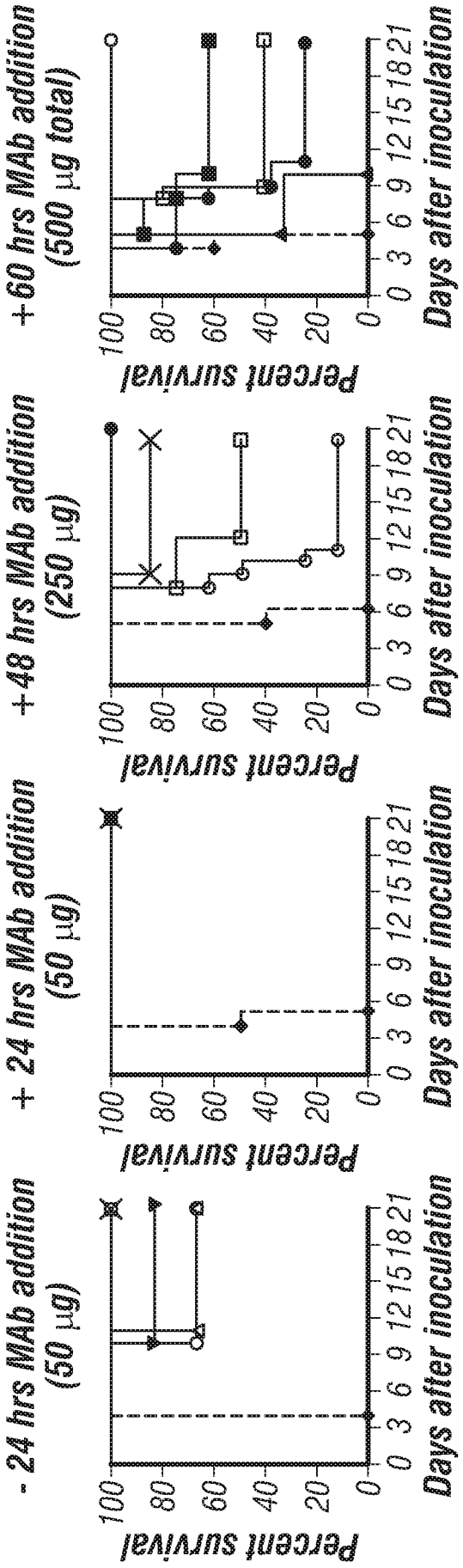


FIG. 3A FIG. 3B FIG. 3C FIG. 3D

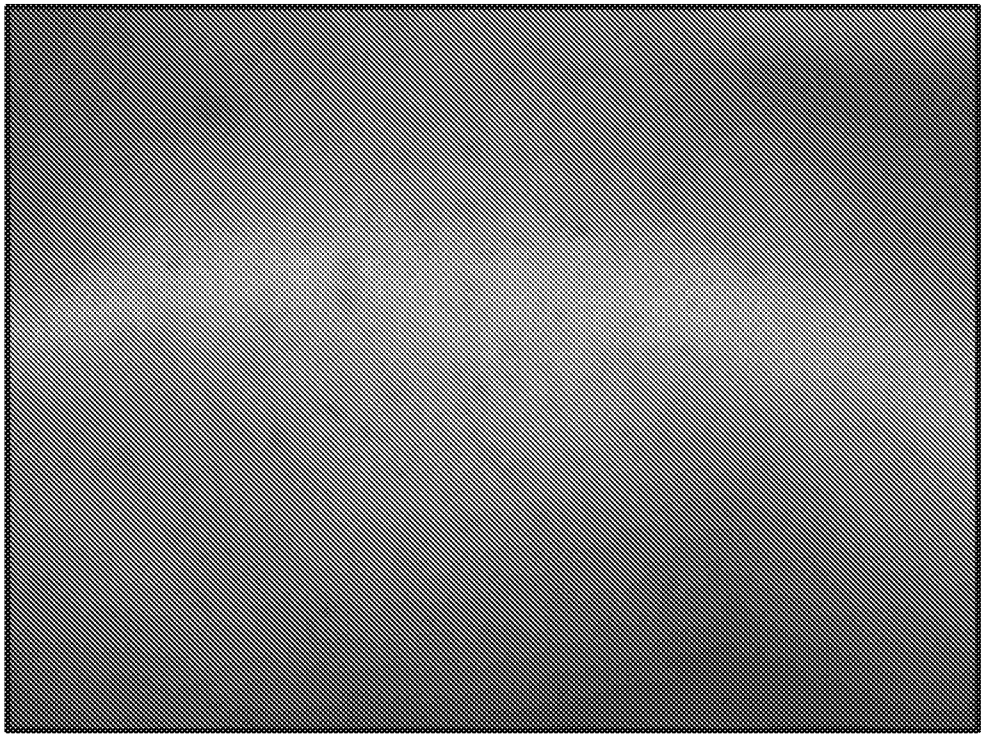


FIG. 4

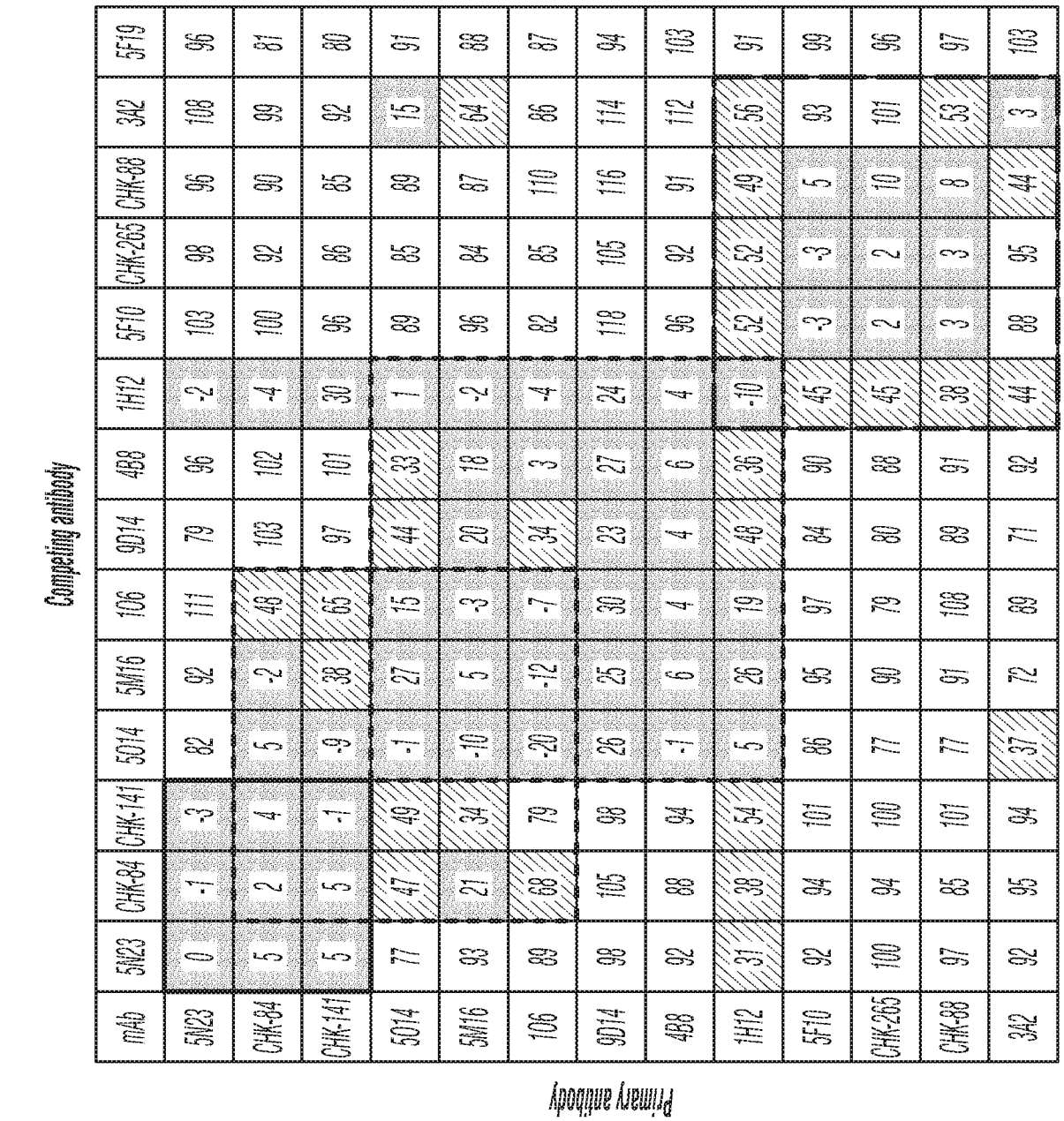

Primary antibody
Competing antibody
mAb
5N23
CHK-84
CHK-141
5D14
5M16
10G6
9D14
4B8
1H12
5F10
CHK-265
CHK-88
3A2
5F19
Domain(s) identified by mutagenesis studies
5N23 0 -1 -3 82 92 111 79 96 -2 103 98 96 108 96
CHK-84 5 2 4 5 -2 48 103 102 -4 100 92 90 99 81
CHK-141 5 5 -1 -9 38 65 97 101 30 96 86 85 92 80
5D14 77 47 49 -1 27 15 44 33 1 89 85 89 15 91
5M16 93 21 34 -10 5 -3 20 18 -2 96 84 87 64 88
10G6 89 68 79 -20 -12 -7 34 3 -4 82 85 110 86 87
9D14 98 105 98 26 25 30 23 27 24 118 105 116 114 94
4B8 92 88 94 -1 6 4 4 6 4 96 92 91 112 103
1H12 31 38 54 5 26 19 46 36 -10 52 52 49 56 91
5F10 92 94 101 86 95 97 84 90 45 -3 -3 5 93 99
CHK-265 100 94 100 77 90 79 80 88 45 2 2 10 101 96
CHK-88 97 85 101 77 91 108 89 91 38 3 3 8 53 97
3A2 92 95 94 37 72 89 71 92 44 88 95 44 3 103
Domain(s) identified by mutagenesis studies
DA, Arch
DA
DA
NR
DA
DA
NotR
NR
DA/DB Arch
DB
DB
DB

FIG. 5

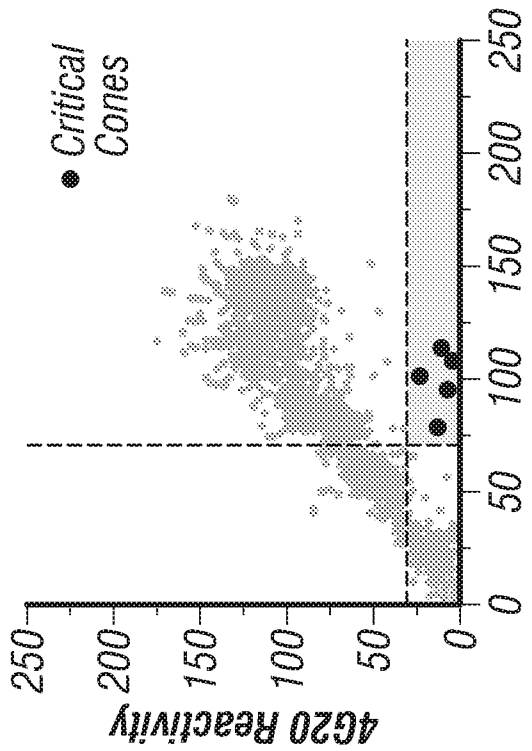


FIG. 6B

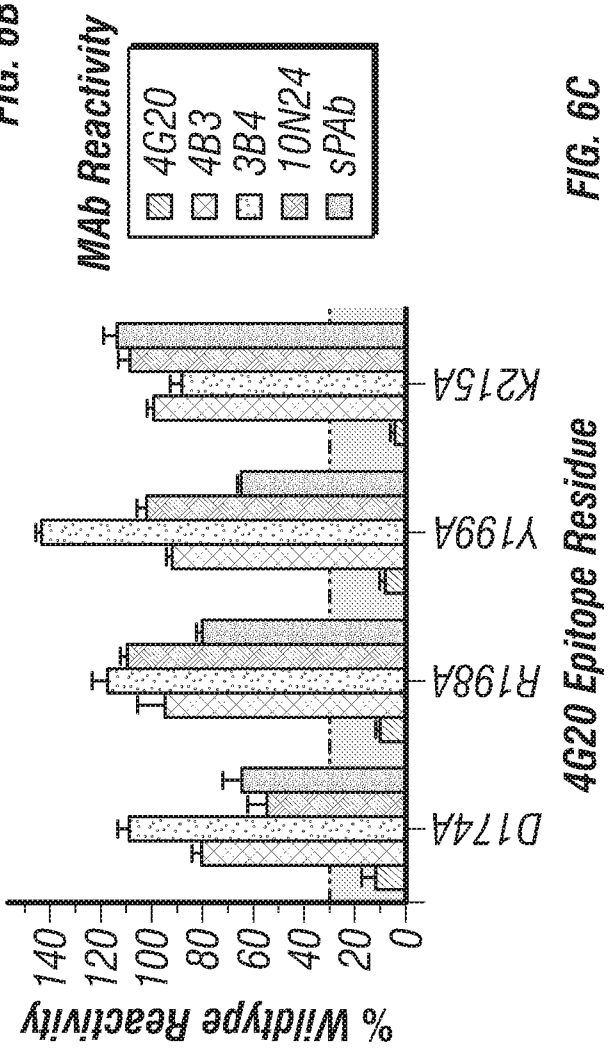


FIG. 6C

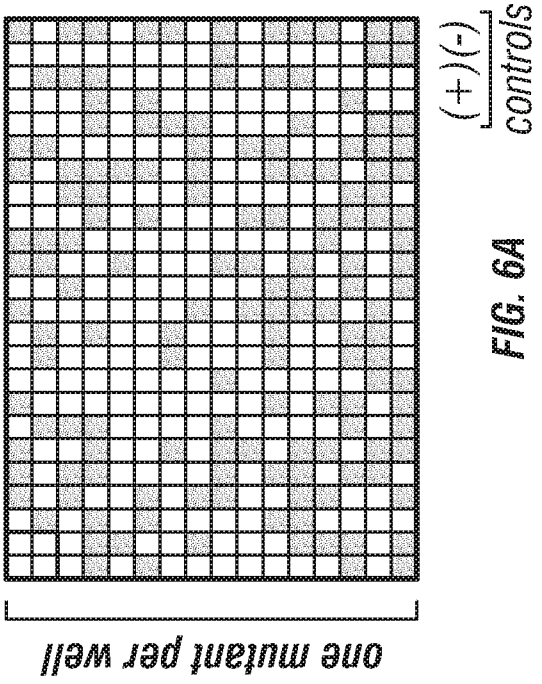
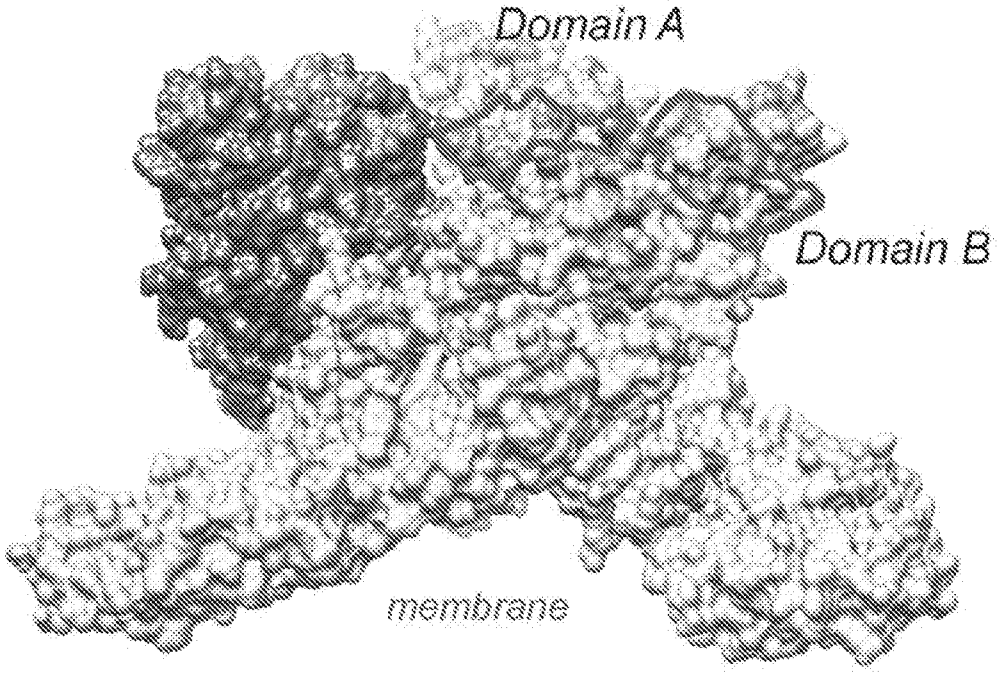
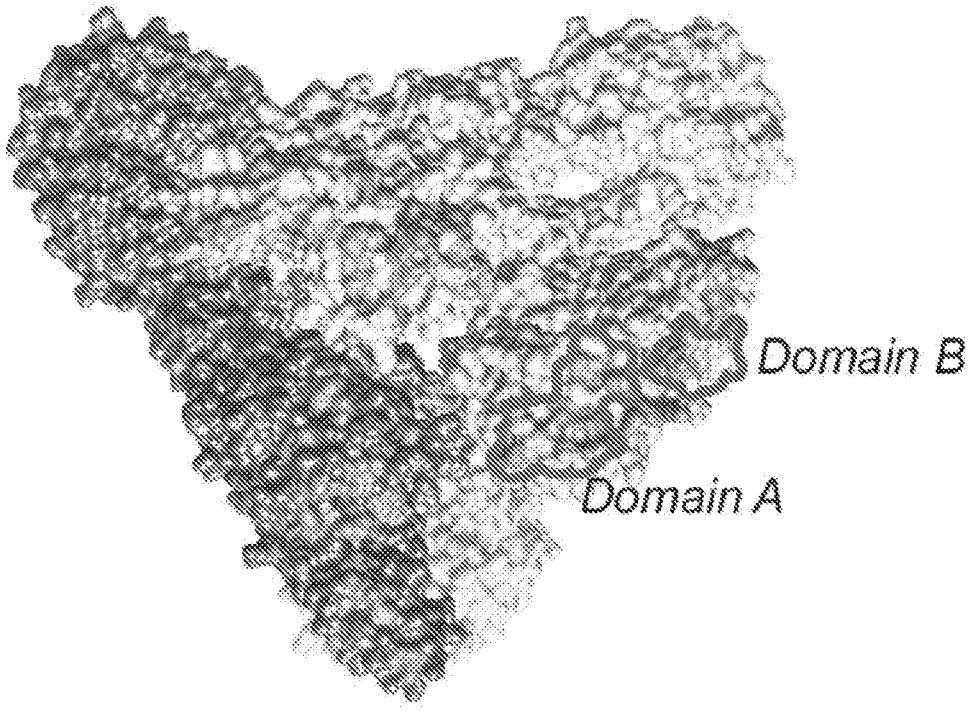


FIG. 6A



trimer - side view

FIG. 6E



trimer - top down view

FIG. 6F

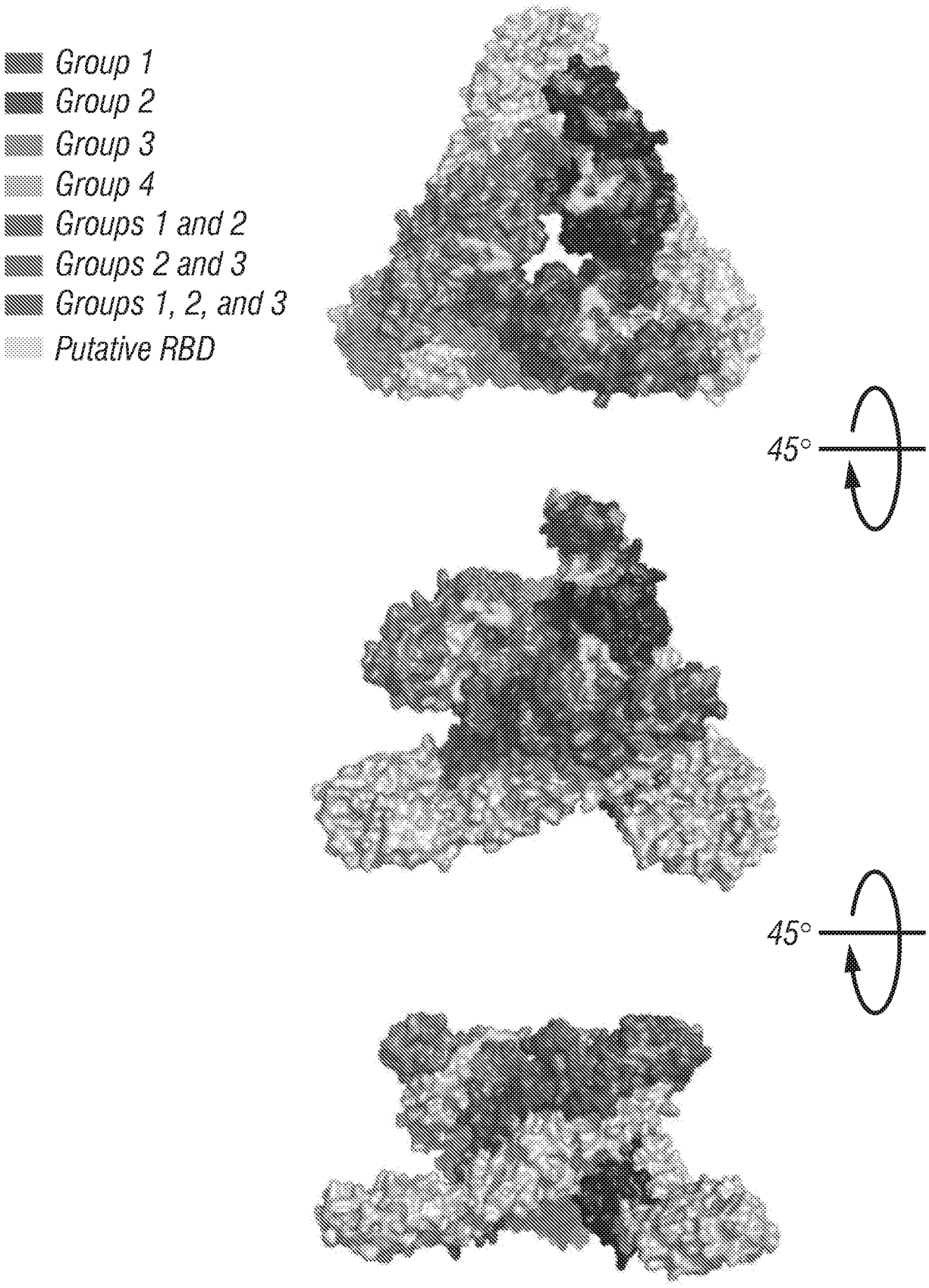

Group 1
Group 2
Group 3
Group 4
Groups 1 and 2
Groups 2 and 3
Groups 1, 2, and 3
Putative RBD
45°
45°

FIG. 7

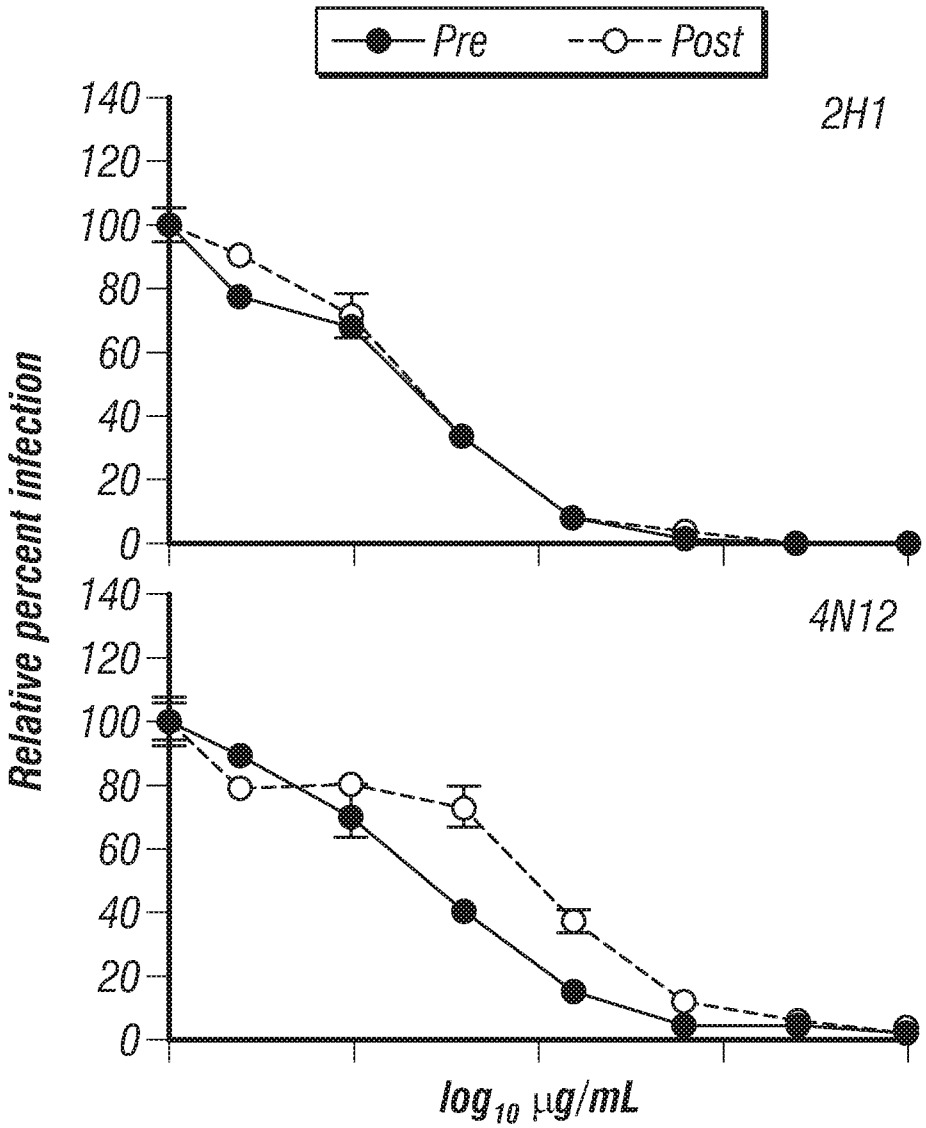

Pre
Post
2H1
4N12
140
120
100
80
60
40
20
0
Relative percent infection
log10 µg/mL

FIG. 8

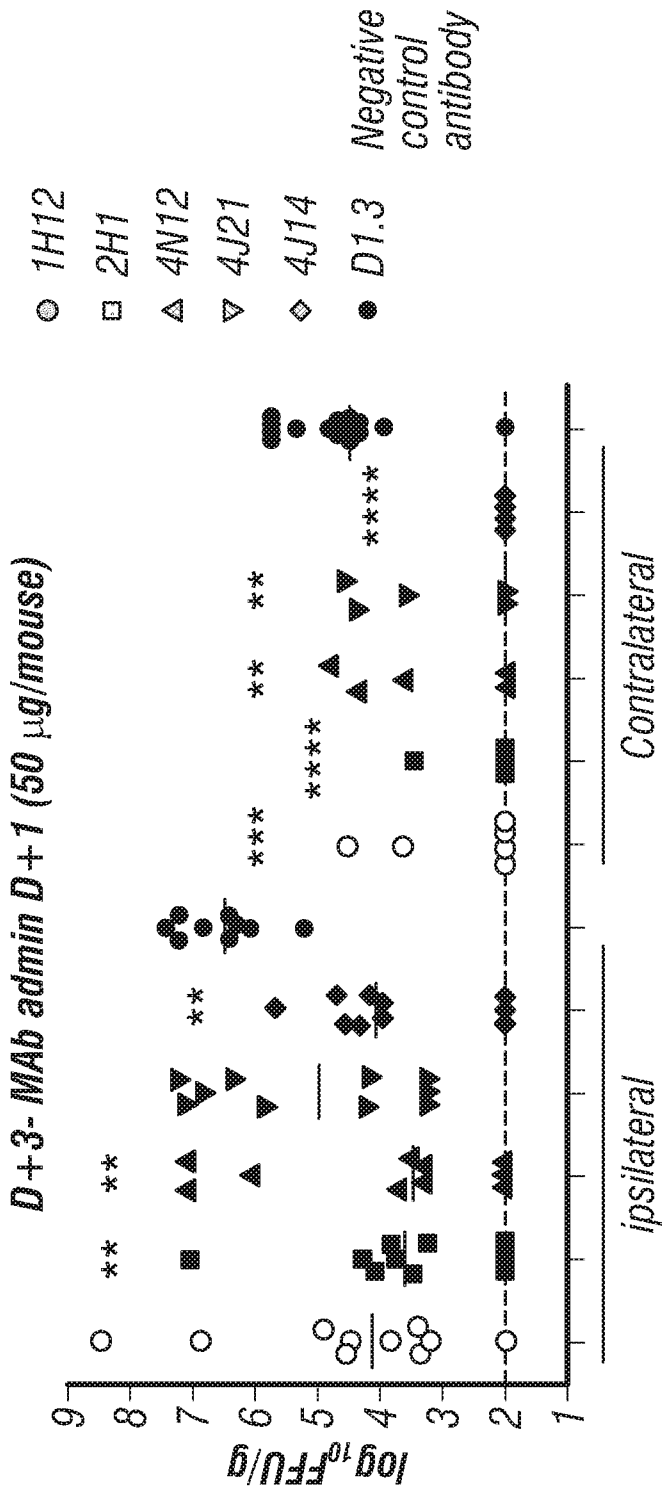

D+3- MAb admin D+1 (50 µg/mouse)
log10FFU/g
1H12
2H1
4N12
4J21
4J14
D1.3
Negative control antibody
Krustal-Wallis test for each tissue compared to D1.3
ipsilateral
Contralateral

FIG. 9

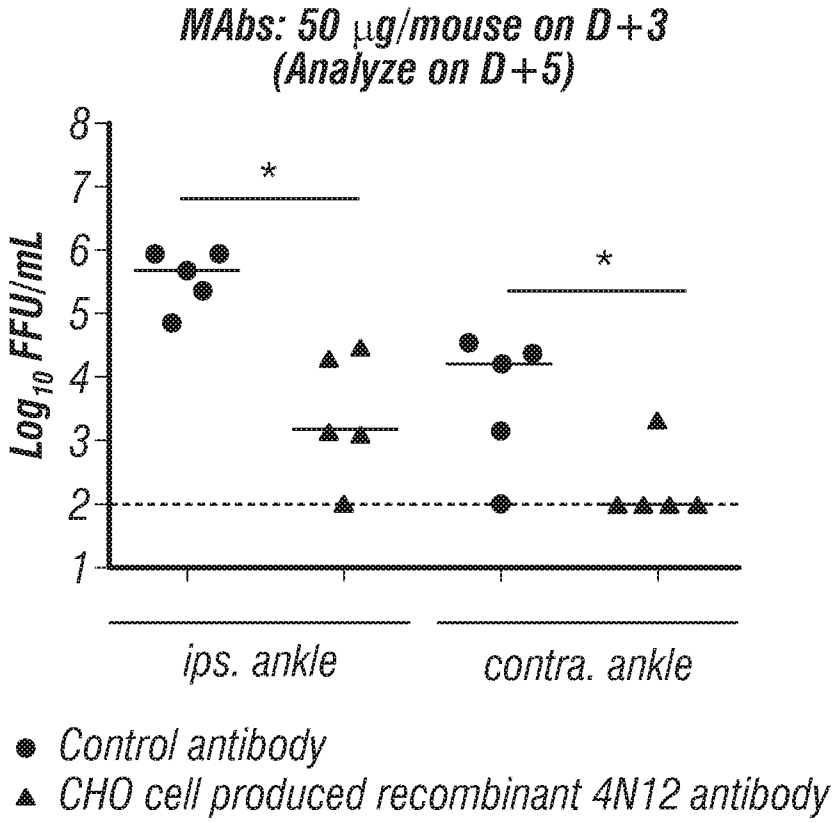

MAbs: 50 μg/mouse on D+3
(Analyze on D+5)
Log10 FFU/mL
8
7
6
5
4
3
2
1
*
*
ips. ankle
contra. ankle
Control antibody
CHO cell produced recombinant 4N12 antibody

FIG. 10

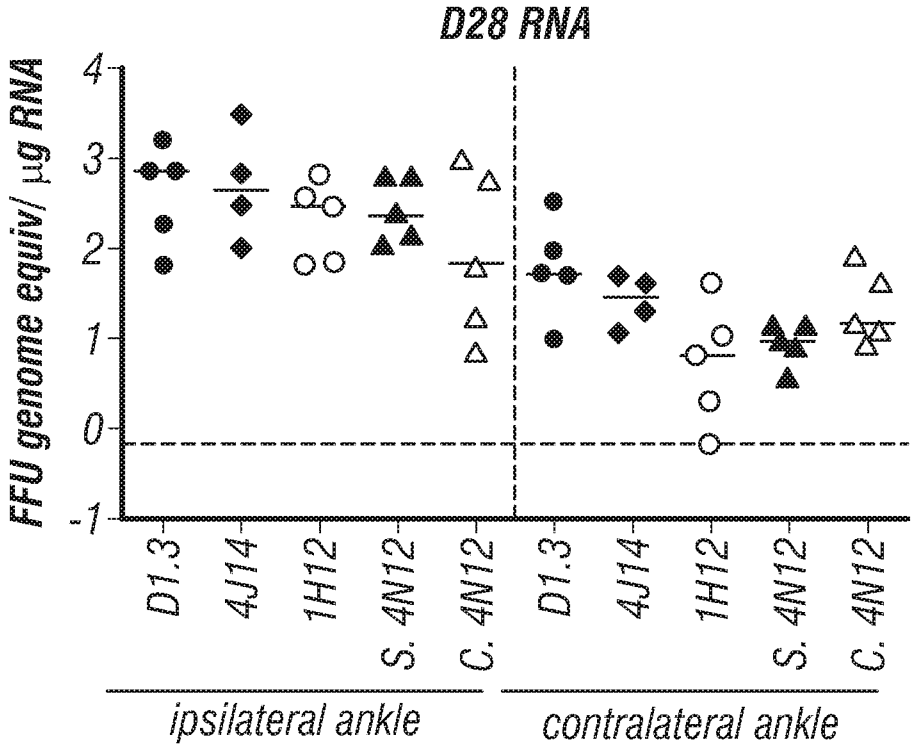

D28 RNA
FFU genome equiv/ μg RNA
4
3
2
1
0
-1
D1.3
4J14
1H12
S. 4N12
C. 4N12
D1.3
4J14
1H12
S. 4N12
C. 4N12
ipsilateral ankle
contralateral ankle
D1.3 is a negative control antibody

FIG. 11

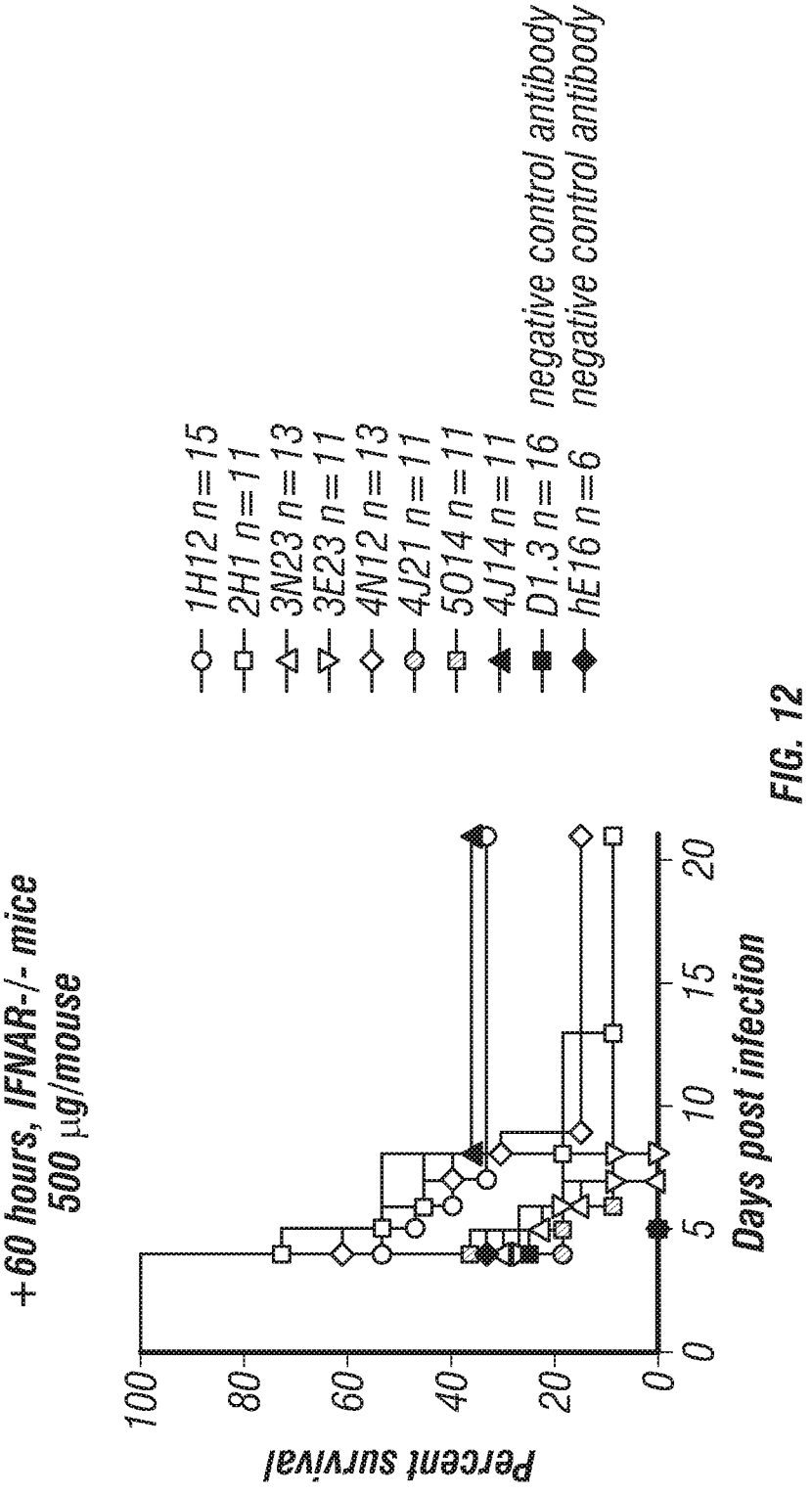

+60 hours, IFNAR-/- mice
500 µg/mouse
Percent survival
Days post infection
0
20
40
60
80
100
0
5
10
15
20
1H12 n=15
2H1 n=11
3N23 n=13
3E23 n=11
4N12 n=13
4J21 n=11
5O14 n=11
4J14 n=11
D1.3 n=16
hE16 n=6
negative control antibody
negative control antibody

FIG. 12

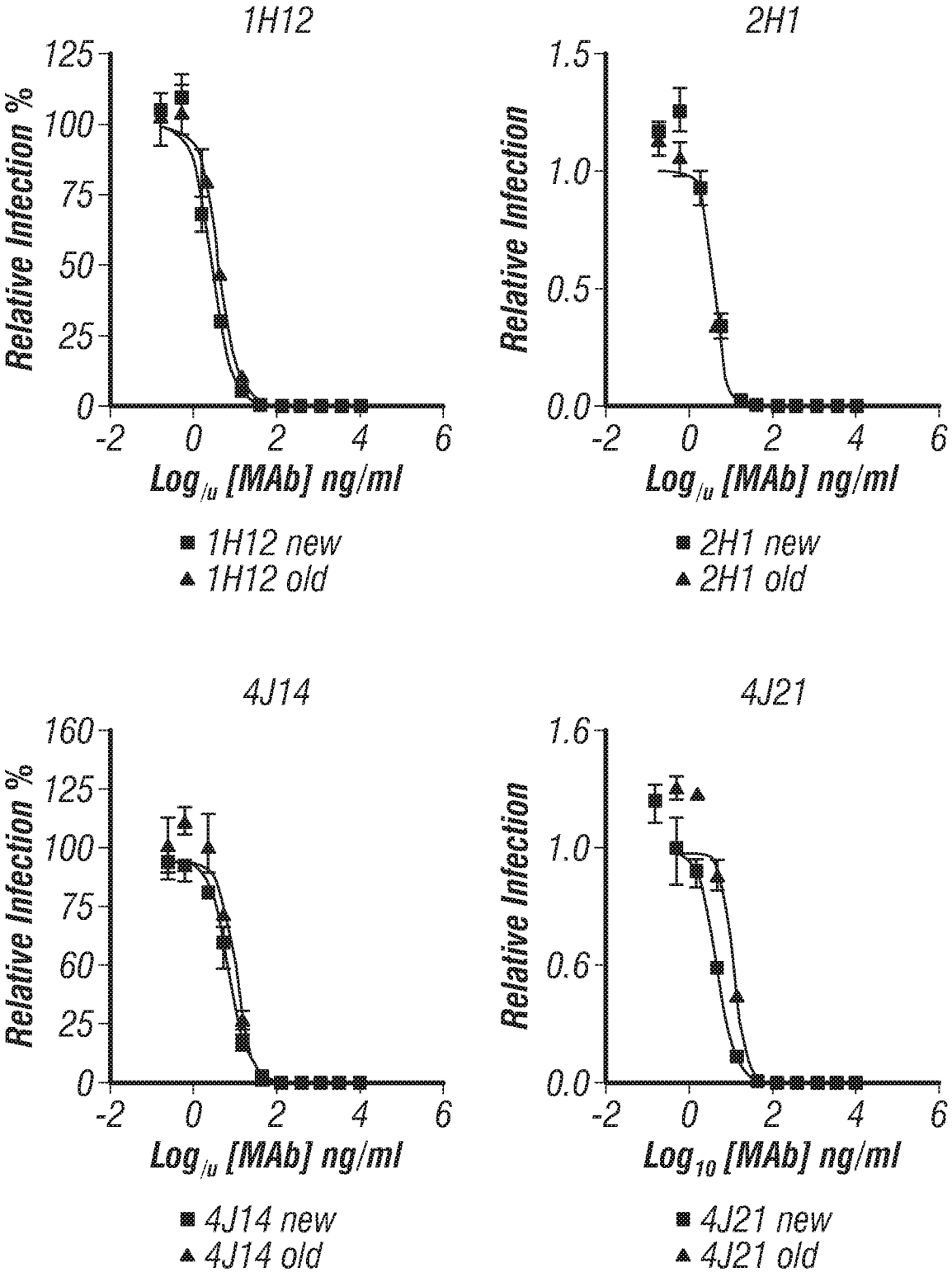

1H12
Relative Infection %
125
100
75
50
25
0
-2
0
2
4
6
Log10 [MAb] ng/ml
1H12 new
1H12 old
2H1
Relative Infection
1.5
1.0
0.5
0.0
-2
0
2
4
6
Log10 [MAb] ng/ml
2H1 new
2H1 old
4J14
Relative Infection %
160
125
100
75
60
25
0
-2
0
2
4
6
Log10 [MAb] ng/ml
4J14 new
4J14 old
4J21
Relative Infection
1.6
1.0
0.6
0.0
-2
0
2
4
6
Log10 [MAb] ng/ml
4J21 new
4J21 old

FIG. 13

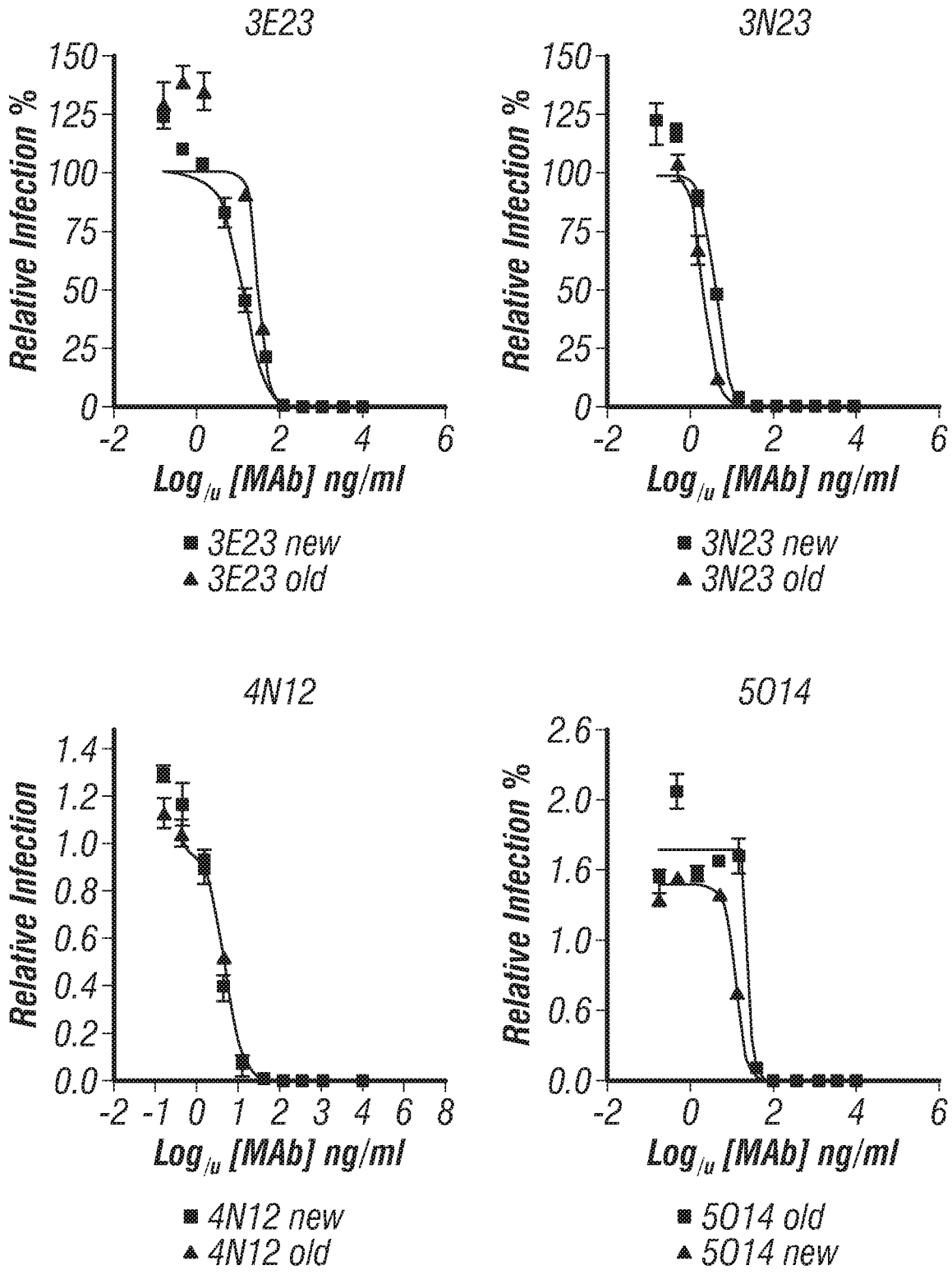

3E23
Relative Infection %
150
125
100
75
50
25
0
-2
0
2
4
6
Log10 [MAb] ng/ml
3E23 new
3E23 old
3N23
Relative Infection %
150
125
100
75
50
25
0
-2
0
2
4
6
Log10 [MAb] ng/ml
3N23 new
3N23 old
4N12
Relative Infection
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-2 -1 0 1 2 3 4 6 8
Log10 [MAb] ng/ml
4N12 new
4N12 old
5014
Relative Infection %
2.6
2.0
1.6
1.0
0.6
0.0
-2
0
2
4
6
Log10 [MAb] ng/ml
5014 old
5014 new

FIG. 13
(Cont'd)

Clone	Hybridoma-produced mAb ('old')	Recombinant CHO cell-produced mAb ('new')
1H12	4.2	2.7
2H1	4	3.8
(3E)23	34	13.8
3N23	2.1	4.5
4J14	8.6	5.7
4J21	11.4	4.8
4N12	4.8	5
5M16	5.9	1,094
5(O)14	14.3	34.8

FIG. 14

Chikungunya virus E1/E2 alignment:

ECSA Genotypes:	LR2006 S27 SL15649
Asian Genotypes:	181/25 99659
West African Genotype:	IbH35

Aligned sequences are shown as Protein_Strain_Genbank accession number

FIG. 15

```
CLUSTAL O(1.2.1) multiple sequence alignment

E1_S27_NC004162.2          TACGAACACGTAACAGTGATCCCGAACACGGTGGGAGTACCGTATAAGACTCTAGTCAAC
E1_SL15649_GU189061.1      TACGAACACGTAACAGTGATCCCGAACACGGTGGGAGTACCGTATAAGACTCTAGTCAAT
E1_LR2006_KT449801.1       TACGAACACGTAACAGTGATCCCGAACACGGTGGGAGTACCGTATAAGACTCTAGTCAAT
E1_181/25_L37661.3         TACGAACACGTAACAGTGATCCCGAACACGGTGGGAGTACCGTATAAGACTCTAGTCAAC
E1_99659_KJ451624.1        TACGAACACGTAACAGTGATCCCGAACACGGTGGGAGTACCGTATAAGACTCTAGTCAAC
E1_IbH35_HM045786.1        TACGAACACGTAACAGTGATCCCGAACACGGTGGGAGTACCGTATAAGACTCTTGTCAAC
                           ************************************************:*****

E1_S27_NC004162.2          AGACCGGGCTACAGCCCCATGGTACTGGAGATGGAGCTACTGTCAGTCACTTTGGAGCCA
E1_SL15649_GU189061.1      AGACCTGGCTACAGCCCCATGGTATTGGAGATGGAACTACTGTCAGTCACTTTGGAGCCA
E1_LR2006_KT449801.1       AGACCTGGCTACAGCCCCATGGTATTGGAGATGGAACTACTGTCAGTCACTTTGGAGCCA
E1_181/25_L37661.3         AGACCGGGCTACAGCCCCATGGTACTGGAGATGGAGCTTCTGTCAGTCACTTTGGAGCCA
E1_99659_KJ451624.1        AGACCGGGCTACAGCCCCATGGTATTGGAGATGGAGCTTCTGTCTGTCACCTTGGAACCA
E1_IbH35_HM045786.1        AGACCGGGTTACAGCCCCATGGTATTGGAGATGGAGCTACAATCGGTCACCTTGGAACCA
                           ***** ** *************** **********.**:*:.** ***** *****.***

E1_S27_NC004162.2          ACGCTATCGCTTGATTACATCACGTGCGAATACAAAACCGTCATCCCGTCTCCGTACGTG
E1_SL15649_GU189061.1      ACACTATCGCTTGATTACATCACGTGCGAGTACAAAACCGTCATCCCGTCTCCGTACGTG
E1_LR2006_KT449801.1       ACACTATCGCTTGATTACATCACGTGCGAGTACAAAACCGTCATCCCGTCTCCGTACGTG
E1_181/25_L37661.3         ACGCTATCGCTTGATTACATCACGTGCGAGTATAAAACCGTCATCCCGTCTCCGTACGTG
E1_99659_KJ451624.1        ACGCTATCGCTTGATTACATCACGTGCGAGTATAAAACCGTTATCCCGTCTCCGTACGTG
E1_IbH35_HM045786.1        ACACTGTCACTTGACTACATCACGTGCGAGTACAAAACTGTCATCCCGTCCCCGTACGTG
                           **.**.**.***** ************.** ***** ** ***** ** *********

E1_S27_NC004162.2          AAATGCTGCGGTACAGCAGAGTGCAAGGACAAAAACCTACCTGACTACAGCTGTAAGGTC
E1_SL15649_GU189061.1      AAGTGCTGCGGTACAGCAGAGTGCAAGGACAAAAACCTACCTGACTACAGCTGTAAGGTC
E1_LR2006_KT449801.1       AAGTGCTGCGGTACAGCAGAGTGCAAGGACAAAAACCTACCTGACTACAGCTGTAAGGTC
E1_181/25_L37661.3         AAATGCTGCGGTACAGCAGAGTGCAAGGACAAGAGCCTACCTGATTACAGCTGTAAGGTC
E1_99659_KJ451624.1        AAATGCTGCGGTACAGCAGAGTGTAAGGACAAGAGCCTACCTGATTACAGCTGTAAGGTC
E1_IbH35_HM045786.1        AAGTGCTGTGGTACAGCAGAGTGCAAGGACAAGAGCCTACCAGACTACAGCTGCAAGGTC
                           **.***** ************** ********.*.******:** ******** ******
```

FIG. 15 (Cont'd)

```
E1_S27_NC004162.2          TTCACCGGCGTCTACCCATTATGTGGGGCGGCGCCTACTGCTTCTGCGACGCTGAAAAC
E1_SL15649_GU189061.1      TTCACCGGCGTCTACCCATTTATGTGGGGCGGCGCCTACTGCTTCTGCGACGCTGAAAAC
E1_LR2006_KT449801.1       TTCACCGGCGTCTACCCATTTATGTGGGGCGGCGCCTACTGCTTCTGCGACGCTGAAAAC
E1_181/25_L37661.3         TTCACCGGCGTCTACCCATTCATGTGGGGCGGCGCCTACTGCTTCTGCGACACTGAAAAT
E1_99659_KJ451624.1        TTCACCGGCGTCTACCCATTCATGTGGGGCGGCGCCTACTGCTTCTGCGACACCGAAAAT
E1_IbH35_HM045786.1        TTTACTGGAGTCTACCCATTTATGTGGGGCGGCGCCTACTGCTTTTGCGACGCCGAAAAT
                           ** ** **.*********** ********************** ******.* *****

E1_S27_NC004162.2          ACGCAATTGAGCGAAGCACACATGTGGAGAAGTCCGAATCATGCAAAACAGAATTTGCATCA
E1_SL15649_GU189061.1      ACGCAGTTGAGCGAAGCACACATGTGGAGAAGTCCGAATCATGCAAAACAGAATTTGCATCA
E1_LR2006_KT449801.1       ACGCAGTTGAGCGAAGCACACGTGGAGAAGTCCGAATCATGCAAAACAGAATTTGCATCA
E1_181/25_L37661.3         ACGCAATTGAGCGAAGCACACATGTGGAGAAGTCCGAATCATGCAAAACAGAATTTGCATCA
E1_99659_KJ451624.1        ACGCAATTGAGCGAAGCACACATGTGGAGAAGTCCGAATCATGCAAAACAGAATTTGCATCA
E1_IbH35_HM045786.1        ACGCAATTGAGCGAGGCACACATGTAGAGAAAATCTGAATCTTGCAAAACAGAGTTTGCATCG
                           ******.*********.****** **.******.** ******:********.********.

E1_S27_NC004162.2          GCATACAGGGCTCATACCGCATCCGCATCAGCTAAGCTCCGCGTCCTTTACCAAGGAAAT
E1_SL15649_GU189061.1      GCATACAGGGCTCATACCGCATCTGCATCAGCTAAGCTCCGCGTCCTTTACCAAGGAAAT
E1_LR2006_KT449801.1       GCATACAGGGCTCATACCGCATCTGCATCAGCTAAGCTCCGCGTCCTTTACCAAGGAAAT
E1_181/25_L37661.3         GCATATAGGGCTCATACCGCATCCGCATCAGCTAAGCTCCGCGTCCTTTACCAAGGAAAT
E1_99659_KJ451624.1        GCATACAGGGCTCATACCGCATCCGCATCAGCTAAGCTCCGCGTCCTTTACCAAGGAAAT
E1_IbH35_HM045786.1        GCCTACAGAGCCCACACCGCATCCGCGTCGGCGAAGCTCCGCGTCCTTTACCAAGGAAAC
                           **.*** **.*.** ** ********** **.**.** ********************

E1_S27_NC004162.2          AACATCACTGTAACTGCCTATGCCAAACGGCGACCATGCCGTCACAGTTAAGGACGCCAAA
```

FIG. 15 (Contd)

```
E1_SL15649_GU189061.1   AACATCACTGTAACTGCCTATGCCAAACGGCGACCATGCCGTCACAGTTAAGGACGCCAAA
E1_LR2006_KT449801.1    AACATCACTGTAACTGCCTATGCAAACGGCGACCATGCCGTCACAGTTAAGGACGCCAAA
E1_181/25_L37661.3      AATGTTACTGTATCTGCTTATGCAAACGGCGATCATGCCGTCACAGTTAAGGACGCTAAA
E1_99659_KJ451624.1     AATATCACTGTGGCTGCTTATGCAAACGGCGACCATGCCGTCACAGTTAAGGACGCTAAA
E1_IbH35_HM045786.1     AACATTACTGTAGCTGCCTACGGCTAACGGCGACCATGCCGTCACAGTAAAGGACGCCAAG
                        ** .* ****** ***** ** **:********** **********:********* **.

E1_S27_NC004162.2       TTCATTGTGGGGCCAATGTCTTCAGCCTGGACACCTTTTGACAACAAATCGTGGTGTAC
E1_SL15649_GU189061.1   TTCATTGTGGGGCCAATGTCTTCAGCCTGGACACCTTTCGACAACAAATTGTGGTGTAC
E1_LR2006_KT449801.1    TTCATTGTGGGGCCAATGTCTTCAGCCTGGACACCTTTCGACAACAAATTGTGGTGTAC
E1_181/25_L37661.3      TTCATTGTGGGGCCAATGTCTTCAGCCTGGACACCTTTTGACAATAAAATCGTGGTGTAC
E1_99659_KJ451624.1     TTCATAGTGGGGCCAATGTCTTCAGCCTGGACACCTTTCGACAATAAAATCGTGGTGTAC
E1_IbH35_HM045786.1     TTTGTCGTGGGGACCAATGTCCTCCGCCTGGACACCTTTTGACAACAAAATCGTGGTGTAC
                        ** .* ****** .********** ** .********** ****** ****** **********

E1_S27_NC004162.2       AAAGGTGACGTTTACAACATGGACTACCCGCCCTTTGGCGCAGGAAGACCAGGACAATTT
E1_SL15649_GU189061.1   AAAGGTGACGTCTATAACATGGACTACCCGCCCTTTGGCGCAGGAAGACCAGGACAATTT
E1_LR2006_KT449801.1    AAAGGTGACGTCTATAACATGGACTACCCGCCCTTTGGCGCAGGAAGACCAGGACAATTT
E1_181/25_L37661.3      AAAGGCGACGTCTACAACATGGACTACCCGCCCTTCGGCGCAGGAAGACCAGGACAATTT
E1_99659_KJ451624.1     AAAGGCGACGTCTACAACATGGACTACCCGCCCTTCGGCGCAGGAAGACCAGGACAATTT
E1_IbH35_HM045786.1     AAAGGCGACGTCTACAACATGGACTACCCACCTTTTGGCGCAGGAAGACCAGGACAATTT
                        ****** ****** ** ********************.** ** ********************

E1_S27_NC004162.2       GGCGATATCCAAAGTCGCACGCCTGAGAGCAAAGACGTCTATGCTAACACACAACTGGTA
E1_SL15649_GU189061.1   GGCGATATCCAAAGTCGGCACACCTGAGAGTAAAGACGTCTATGCTAATACACAACTGGTA
E1_LR2006_KT449801.1    GGCGATATCCAAAGTCGCACACCTGAGAGTAAAGACGTCTATGCTAATACACAACTGGTA
E1_181/25_L37661.3      GGCGACATCCAAAGTCGCACGCCTGAGAGCGAAGACGTCTATGCTAACACACAACTGGTA
E1_99659_KJ451624.1     GGCGACATCCAAAGTCGCACGCCTGAGAGCGAAGACGTCTATGCTAATGCACACAACTGGTA
E1_IbH35_HM045786.1     GGTGACATTCAAAGTCGTACACCGGAAAGTAAAGACGTTTATGCCAACACTCAGTTGGTA
                        ** ** ** ********** **.** **.** .******** ****** ** **:**. *****
```

FIG. 15 (Contd)

```
E1_S27_NC004162.2          CTGCAGAGACCGGCTGCGGGTACACGTGCCATACTCTCAGGCACCATCTGGCTTT
E1_SL15649_GU189061.1      CTGCAGAGACCGGCTGCGGGTACACGTGCCATACTCTCAGGCACCATCTGGCTTT
E1_LR2006_KT449801.1       CTGCAGAGACCGGCTGTGGGTACACGTGCCATACTCTCAGGCACCATCTGGCTTT
E1_181/25_L37661.3         CTGCAGAGACCGTCCGCGGGTACACGTGCCGTACTCTCAGGCACCATCTGGCTTC
E1_99659_KJ451624.1        CTGCAGAGACCGTCCGCGGGTACACGTGCCGTACTCTCAGGCACCATCTGGCTTC
E1_IbH35_HM045786.1        CTACAGAGGCCAGCAGGCACGGTACATGTACCATACTCTCAGGCACCATCTGGCTTC
                           **.*******.***. * *  .** ******.** **.**.**********.****

E1_S27_NC004162.2          AAGTATTGGTTAAAAGAACGAGGGGCGTCGCTACAGCACACAGCACCATTTGGCTGCCAA
E1_SL15649_GU189061.1      AAGTATTGGCTAAAAGAACGCGGGGCGTCACTGCAGCACACAGCACCATTTGGCTGCCAA
E1_LR2006_KT449801.1       AAGTATTGGCTAAAAGAACGCGGGGCGTCGCTGCAGCACACAGCACCATTTGGCTGCCAA
E1_181/25_L37661.3         AAGTATTGGCTAAAAGAACGAGGGGCGTCGCTGCAGCACACAGCACCATTTGGCTGTCAA
E1_99659_KJ451624.1        AAGTATTGGCTAAAAGAACGAGGGGCGTCGCTGCAGCACACAGCACCATTTGGCTGTCAA
E1_IbH35_HM045786.1        AAGTATTGGCTGAAGGAACGAGGAGCATCGCTACAGCACACGGCACCGTTCGGTTGCCAG
                           ********** *.**.*******.**.**.**.**.**.**********.******.** ** ** **.

E1_S27_NC004162.2          ATAGCAACAAACCCGGTAAGAGCGATGAACTGCGCCGTAGGGAACATGCCCATCTCCATC
E1_SL15649_GU189061.1      ATAGCAACAAACCCGGTAAGAGCGGTGAACTGCGCCGTAGGGAACATGCCCATCTCCATC
E1_LR2006_KT449801.1       ATAGCAACAAACCCGGTAAGAGCGGTGAACTGCGCCGTAGGGAACATGCCCATCTCCATC
E1_181/25_L37661.3         ATAGCAACAAACCCGGTAAGAGCGATGAACTGCGCCGTAGGGAACATGCCTATCTCCATC
E1_99659_KJ451624.1        ATAGCAACAAACCCGGTAAGAGCGATGAACTGCGCCGTAGGGAACATGCCTATCTCCATC
E1_IbH35_HM045786.1        ATTGCGACAAACCCGGTAAGAGCTGTAAATTGCGCCTGTGGGGAACATACCAATTTCCATC
                           **:**.*********************  .*.** ***** **.*********.** ** ******

E1_S27_NC004162.2          GACATACCGGATGCGGCCTTCACTAGGGTCGTCGACGCGCCCTCTTTAACGGACATGTCA
E1_SL15649_GU189061.1      GACATACCGGAAGCGGCCTTCACTAGGGTCGTCGACGCGCCCTCTTTAACGGACATGTCG
E1_LR2006_KT449801.1       GACATACCGGAAGCGGCCTTCACTAGGGTCGTCGACGCGCCCTCTTTAACGGACATGTCG
E1_181/25_L37661.3         GACATACCGGACGCGGCCTTCACTAGGGTCGTCGACGCGCCATCTTTAACGGACATGTCG
E1_99659_KJ451624.1        GACATACCGGACGCGGCCTTTACCAGGGTCGTCGACGCGCCATCTTTAACGGACATGTCG
E1_IbH35_HM045786.1        GACATACCGGATGCGGCCTTTACTAGGGTTGTCGATGCACCCTCTGTAACGGACATGTCA
                           ********** ********** ** ****** ****** **.**.*** ************.
```

FIG. 15 (Contd)

```
E1_S27_NC004162.2          TGCGAGGTACCAGCCTGCACCCATTCCTCAGACTTTGGGGGCGTCGCCATTATTAAATAT
E1_SL15649_GU189061.1      TGCGAGGTACTAGCCTGCACCCATTCCTCAGACTTTGGGGGCGTCGCCATTATTAAATAT
E1_LR2006_KT449801.1       TGCGAGGTACCAGCCTGCACCCATTCCTCAGACTTTGGGGGCGTCGCCATTATTAAATAT
E1_181/25_L37661.3         TGTGAGGTACCAGCCTGCACCCACTCCTCAGACTTTGGGGGCGTAGCCATCATTAAATAT
E1_99659_KJ451624.1        TGTGAGGTATCAGCCTGCACCCATTCCTCAGACTTTGGGGGCGTAGCCATCATTAAATAT
E1_IbH35_HM045786.1        TGCGAAGTACCAGCCTGCACTCACTCCTCCGACTTTGGGGGCGTCGCCATCATTAAATAT
                           ** **.*.****  ********** ** ****** *********.****** ** ******

E1_S27_NC004162.2          GCAGTCAGCAAGAAAGGCAAGTGTGCGGTGCATTCGATGACCAACGCCGTCACTATCCGG
E1_SL15649_GU189061.1      GCAGCCAGCAAGAAAGGCAAGTGTGCGGTGCATTCGATGACTAACGCCGTCACTATTCGG
E1_LR2006_KT449801.1       GCAGCCAGCAAGAAAGGCAAGTGTGCGGTGCATTCGATGACTAACGCCGTCACTATTCGG
E1_181/25_L37661.3         GCAGCCAGCAAGAAAGGCAAGTGTGCGGTGCATTCGATGACTAACGCCGTCACTATTCGG
E1_99659_KJ451624.1        GCAGCCAGTAAGAAAGGCAAGTGTGCAGTGCACTCGATGACTAACGCCGTCACTATTCGG
E1_IbH35_HM045786.1        ACAGCTAGCAAGAAAGGTAAATGTGCAGTACATTCGATGACCAACGCCGTTACCATTCGA
                             ****   ** ********** **.******.***.** ********** ** ** **.

E1_S27_NC004162.2          GAAGCTGAGATAGAAGTTGAAGGGAATTCTCAGCTGCAAAATCTCTTTCTCGACGGCCTTG
E1_SL15649_GU189061.1      GAAGCTGAGATAGAAGTTGAAGGGAATTCTCAGCTGCAAAATCTCTTTCTCGACGGCCTTA
E1_LR2006_KT449801.1       GAAGCTGAGATAGAAGTTGAAGGGAATTCTCAGCTGCAAAATCTCTTTCTCGACGGCCTTA
E1_181/25_L37661.3         GAAGCTGAAATAGAAGTAGAAGGGAACTCTCAGTTGCAAATCTCTTTTTCGACGGCCCTA
E1_99659_KJ451624.1        GAAGCTGAAATAGAAGTAGAAGGGAACTCTCAGTTGCAAATCTCTTTTTCGACGGCCCTA
E1_IbH35_HM045786.1        GAAGCCGACGTAGAAGTAGAGGGGAATTCCCAGCTGCAAATATCCTTCTCAACAGCCTTG
                           ****** **  .********:**.****** ** *** ********.** ** **.**.*** *.

E1_S27_NC004162.2          GCCAGCGCCGAATTCCGCGTACAAGTCTGTTCTACACAAGTACACTGTGCAGCCGAGTGC
E1_SL15649_GU189061.1      GCCAGCGCCGAATTCCGCGTACAAGTCTGTTCTACACAAGTACACTGTGCAGCTGAGTGC
E1_LR2006_KT449801.1       GCCAGCGCCGAATTCCGCGTACAAGTCTGTTCTACACAAGTACACTGTGCAGCCGAGTGC
E1_181/25_L37661.3         GCCAGCGCCGAATTCCGCGTACAAGTCTGTTCTACACAAGTACACTGTGCAGCCGAGTGC
E1_99659_KJ451624.1        GCCAGCGCCGAATTTCGCGTACAAGTCTGTTCTACACAAGTACACTGTGCAGCCGAGTGC
E1_IbH35_HM045786.1        GCAAGCGCCGAGTTTCGCGTGCAAGTGTGCTCCACACAAGTACACTGCGGCAGCCGCATGC
                           **.*********.** ******.***** ** ** ********** ****** *.**.***
```

FIG. 15 (Contd)

```
E1_S27_NC004162.2          CACCCTCCGAAGGACCACACATAGTCAACTACCCGGCGTCACATACCACCCTCGGGGTCCAG
E1_SL15649_GU189061.1      CACCCCCCGAAGGACCACACATAGTCAACTACCCGGCGTCACATACCACCCTCGGGGTCCAG
E1_LR2006_KT449801.1       CACCCCCCGAAGGACCACACATAGTCAACTACCCGGCGTCACATACCACCCTCGGGGTCCAG
E1_181/25_L37661.3         CATCCACCGAAAGACCATATAGTCAATTACCCGGCGTCACACACCACCCTCGGGGTCCAA
E1_99659_KJ451624.1        CATCCACCGAAAGACCATATAGTCAATTACCCGGCGTCACACACCACCCTCGGGGTCCAA
E1_IbH35_HM045786.1        CACCCTCCAAAGGACCACACATAGTCAATTACCCAGCATCACACACCACCCTTGGGGTCCAG
                           ** ** ***.**.*.***** ********** ******.**.***** ********** .

E1_S27_NC004162.2          GACATTTCCGCTACGGCGATGTCATGGGTGCAGAAGATCACGGGAGGTGTGGGACTGGTT
E1_SL15649_GU189061.1      GACATCTCCGCTACGGCGATGTCATGGGTGCAGAAGATCACGGGAGGTGTGGGACTGGTT
E1_LR2006_KT449801.1       GACATCTCCGCTACGGCGATGTCATGGGTGCAGAAGATCACGGGAGGTGTGGGACTGGTT
E1_181/25_L37661.3         GACATTTCCGTTACGGCGATGTCATGGGTGCAGAAGATCACGGGAGGTGTGGGACTGGTT
E1_99659_KJ451624.1        GACATTTCCGCTACGGCGATGTCATGGGTGCAGAAGATCACGGGAGGTGTGGGACTGGTT
E1_IbH35_HM045786.1        GATATATCCACAACGGCAATGTCTTGGGTGCAGAAGATTACGGGAGGAGTAGGATTAATT
                           ** ** **** . :****** .****** :********** ********** :**.***. **.**

E1_S27_NC004162.2          GTCGCTGTTGCAGCACTGATTCTAATCGTGGTGCTATGCGTGTCGTTCAGCAGGCAC
E1_SL15649_GU189061.1      GTTGCTGTTGCCGCACTGATTCTAATCGTGGTGCTATGCGTGTCGTTCAGCAGGCAC
E1_LR2006_KT449801.1       GTTGCTGTTGCCGCACTGATTCTAATCGTGGTGCTATGCGTGTCGTTCAGCAGGCAC
E1_181/25_L37661.3         GTCGCTGTTGCAGCACTGATCCTAATCGTGGTGCTATGCGTGTCGTTTAGCAGGCAC
E1_99659_KJ451624.1        GTCGCTGTTGCAGCACTGATCCTAATCGTGGTGCTATGCGTGTCGTTTAGCAGGCAC
E1_IbH35_HM045786.1        GTTGCTGTTGCTGCCTTAATTTTAATTGTGGTGCTATGCGTGTCGTTTAGCAGGCAC
                           ** ********** **. . *.** ***** ********************** **********
```

FIG. 15 (Contd)

```
CLUSTAL O(1.2.1) multiple sequence alignment

E1_IbH35_HM045786.1          YEHVTVIPNTVGVPYKTLVNRPGYSPMVLEMELQSVTLEPTLSLDYITCEYKTVIPSPYV
E1_S27_NC004162.2            YEHVTVIPNTVGVPYKTLVNRPGYSPMVLEMELLSVTLEPTLSLDYITCEYKTVIPSPYV
E1_SL15649_GUI89061.1        YEHVTVIPNTVGVPYKTLVNRPGYSPMVLEMELLSVTLEPTLSLDYITCEYKTVIPSPYV
E1_LR2006_KT449801.1         YEHVTVIPNTVGVPYKTLVNRPGYSPMVLEMELLSVTLEPTLSLDYITCEYKTVIPSPYV
E1_99659_KJ451624.1          YEHVTVIPNTVGVPYKTLVNRPGYSPMVLEMELLSVTLEPTLSLDYITCEYKTVIPSPYV
E1_181/25_L37661.3           YEHVTVIPNTVGVPYKTLVNRPGYSPMVLEMELLSVTLEPTLSLDYITCEYKTVIPSPYV
                             ********************************* ************************

E1_IbH35_HM045786.1          KCCGTAECKDKSLPDYSCKVFTGVYPFMWGGAYCFCDAENTQLSEAHVEKSESCKTEFAS
E1_S27_NC004162.2            KCCGTAECKDKNLPDYSCKVFTGVYPFMWGGAYCFCDAENTQLSEAHVEKSESCKTEFAS
E1_SL15649_GUI89061.1        KCCGTAECKDKNLPDYSCKVFTGVYPFMWGGAYCFCDAENTQLSEAHVEKSESCKTEFAS
E1_LR2006_KT449801.1         KCCGTAECKDKNLPDYSCKVFTGVYPFMWGGAYCFCDAENTQLSEAHVEKSESCKTEFAS
E1_99659_KJ451624.1          KCCGTAECKDKSLPDYSCKVFTGVYPFMWGGAYCFCDTENTQLSEAHVEKSESCKTEFAS
E1_181/25_L37661.3           KCCGTAECKDKSLPDYSCKVFTGVYPFMWGGAYCFCDTENTQLSEAHVEKSESCKTEFAS
                             **********.**************************:**********************

E1_IbH35_HM045786.1          AYRAHTASASAKLRVLYQGNNITVAAYANGDHAVTVKDAKFVVGPMSSAWTPFDNKIVVY
E1_S27_NC004162.2            AYRAHTASASAKLRVLYQGNNITVTAYANGDHAVTVKDAKFIVGPMSSAWTPFDNKIVVY
E1_SL15649_GUI89061.1        AYRAHTASASAKLRVLYQGNNITVTAYANGDHAVTVKDAKFIVGPMSSAWTPFDNKIVVY
E1_LR2006_KT449801.1         AYRAHTASASAKLRVLYQGNNITVTAYANGDHAVTVKDAKFIVGPMSSAWTPFDNKIVVY
E1_99659_KJ451624.1          AYRAHTASASAKLRVLYQGNNITVAAYANGDHAVTVKDAKFIVGPMSSAWTPFDNKIVVY
E1_181/25_L37661.3           AYRAHTASASAKLRVLYQGNNVTVSAYANGDHAVTVKDAKFIVGPMSSAWTPFDNKIVVY
                             **********************:**:****************:******************

E1_IbH35_HM045786.1          KGDVYNMDYPPFGAGRPGQFGDIQSRTPESKDVYANTQLVLQRPAAGTVHVPYSQAPSGF
E1_S27_NC004162.2            KGDVYNMDYPPFGAGRPGQFGDIQSRTPESKDVYANTQLVLQRPAAGTVHVPYSQAPSGF
E1_SL15649_GUI89061.1        KGDVYNMDYPPFGAGRPGQFGDIQSRTPESKDVYANTQLVLQRPAAGTVHVPYSQAPSGF
E1_LR2006_KT449801.1         KGDVYNMDYPPFGAGRPGQFGDIQSRTPESKDVYANTQLVLQRPAVGTVHVPYSQAPSGF
E1_99659_KJ451624.1          KGDVYNMDYPPFGAGRPGQFGDIQSRTPESEDVYANTQLVLQRPSAGTVHVPYSQAPSGF
E1_181/25_L37661.3           KGDVYNMDYPPFGAGRPGQFGDIQSRTPESEDVYANTQLVLQRPSAGTVHVPYSQAPSGF
                             ********************************:*************:.**************
```

FIG. 15 (Cont'd)

```
E1_IbH35_HM045786.1      KYWLKERGASLQHTAPFGCQIATNPVRAVNCAVGNIPISIDIPDAAFTRVVDAPSVTDMS
E1_S27_NC004162.2        KYWLKERGASLQHTAPFGCQIATNPVRAMNCAVGNMPISIDIPDAAFTRVVDAPSLTDMS
E1_SL15649_GUI89061.1    KYWLKERGASLQHTAPFGCQIATNPVRAVNCAVGNMPISIDIPEAAFTRVVDAPSLTDMS
E1_LR2006_KT449801.1     KYWLKERGASLQHTAPFGCQIATNPVRAVNCAVGNMPISIDIPEAAFTRVVDAPSLTDMS
E1_99659_KJ451624.1      KYWLKERGASLQHTAPFGCQIATNPVRAMNCAVGNMPISIDIPDAAFTRVVDAPSLTDMS
E1_181/25_L37661.3       KYWLKERGASLQHTAPFGCQIATNPVRAMNCAVGNMPISIDIPDAAFTRVVDAPSLTDMS
                         ************************:*******:*********:**********:*****

E1_IbH35_HM045786.1      CEVPACTHSSDFGGVAIIKYTASKKGKCAVHSMTNAVTIREADVEVEGNSQLQISFSTAL
E1_S27_NC004162.2        CEVPACTHSSDFGGVAIIKYAVSKKGKCAVHSMTNAVTIREAEIEVEGNSQLQISFSTAL
E1_SL15649_GUI89061.1    CEVLACTHSSDFGGVAIIKYAASKKGKCAVHSMTNAVTIREAEIEVEGNSQLQISFSTAL
E1_LR2006_KT449801.1     CEVPACTHSSDFGGVAIIKYAASKKGKCAVHSMTNAVTIREAEIEVEGNSQLQISFSTAL
E1_99659_KJ451624.1      CEVSACTHSSDFGGVAIIKYAASKKGKCAVHSMTNAVTIREAEIEVEGNSQLQISFSTAL
E1_181/25_L37661.3       CEVPACTHSSDFGGVAIIKYAASKKGKCAVHSMTNAVTIREAEIEVEGNSQLQISFSTAL
                         ***  **********************:.**********************::**********

E1_IbH35_HM045786.1      ASAEFRVQVCSTQVHCAAACHPPKDHIVNYPASHTTLGVQDISTTAMSWVQKITGGVGLI
E1_S27_NC004162.2        ASAEFRVQVCSTQVHCAAECHPPKDHIVNYPASHTTLGVQDISATAMSWVQKITGGVGLV
E1_SL15649_GUI89061.1    ASAEFRVQVCSTQVHCAAECHPPKDHIVNYPASHTTLGVQDISATAMSWVQKITGGVGLV
E1_LR2006_KT449801.1     ASAEFRVQVCSTQVHCAAECHPPKDHIVNYPASHTTLGVQDISATAMSWVQKITGGVGLV
E1_99659_KJ451624.1      ASAEFRVQVCSTQVHCAAECHPPKDHIVNYPASHTTLGVQDISATAMSWVQKITGGVGLV
E1_181/25_L37661.3       ASAEFRVQVCSTQVHCAAECHPPKDHIVNYPASHTTLGVQDISVTAMSWVQKITGGVGLV
                         ************************************.**********************:

E1_IbH35_HM045786.1      VAVAALILIVVLCVSFSRH
E1_S27_NC004162.2        VAVAALILIVVLCVSFSRH
E1_SL15649_GUI89061.1    VAVAALILIVVLCVSFSRH
E1_LR2006_KT449801.1     VAVAALILIVVLCVSFSRH
E1_99659_KJ451624.1      VAVAALILIVVLCVSFSRH
E1_181/25_L37661.3       VAVAALILIVVLCVSFSRH
                         ******************
```

FIG. 15 (Contd)

```
CLUSTAL O(1.2.1) multiple sequence alignment

E2_181/25_L37661.3          AGTATTAAGGACAACTTCAATGTCTATAAAGCCATAAGACCGTACCTAGCTCACTGTCCC
E2_IbH35_HM045786.1         AGTACTAAGGACAATTTTAATGTCTATAAAGCTACAAGACCATATCTAGCTCATTGTCCT
E2_LR2006_KT449801.1        AGCACCAAGGACAACTTCAATGTCTATAAAGCCACAAGACCATACTTAGCTCACTGTCCC
E2_SL15649_GU189061.1       AGCACCAAGGACAACTTCAATGTCTATAAAGCCACAAGACCATACTTAGCTCACTGTCCC
E2_S27_NC004162.2           AGCACCAAGGACAACTTCAATGTCTATAAAGCCACAAGACCATACCTAGCTCACTGTCCC
E2_99659_KJ451624.1         AGTATTAAGGACCACTTCAATGTCTATAAAGCCACAAGACCGTACCTAGCTCACTGTCCC
                            ** *  ******.* ** ************** * ******.**  ******* *****

E2_181/25_L37661.3          GACTGTGGAGAAGGGCACTCGTGCCATAGTCCCGTAGCGCTAGAACGCATCAGAAACGAA
E2_IbH35_HM045786.1         GACTGCGGAGAAGGGCATTCGTGCCACAGCCCTATCGCATTGGAGCGCATCAGAAATGAA
E2_LR2006_KT449801.1        GACTGTGGAGAAGGGCACTCGTGCCATAGTCCCGTAGCACTAGAACGCATCAGAAATGAA
E2_SL15649_GU189061.1       GACTGTGGAGAAGGGCACTCGTGCCATAGTCCCGTAGCACTAGAACGCATCAGAAATGAA
E2_S27_NC004162.2           GACTGTGGAGAAGGGCACTCGTGCCATAGTCCCGTAGCACTAGAACGCATCAGAAATGAA
E2_99659_KJ451624.1         GACTGTGGAGAAGGGCACTCGTGCCATAGTCCCGTAGCGCTAGAACGCATCAGAAACGAA
                            ***** ********** ******** ** ** .*.**. *.**.*********** ***

E2_181/25_L37661.3          GCGACAGACGGGACGCTGAAAATCCAGGTTTCCTTGCAAATCGGAATAAAGACGGATGAT
E2_IbH35_HM045786.1         GCAACGGACGGAACGCTGAAAATCCAGGTCTCTTTGCAGATCGGGATAAAGACAGATGAC
E2_LR2006_KT449801.1        GCGACAGACGGGACGCTGAAAATCCAGGTCTCCTTGCAAATCGGAATAAAGACGGATGAC
E2_SL15649_GU189061.1       GCGACAGACGGGACGCTGAAAATCCAGGTCTCCTTGCAAATCGGAATAAAGACGGACGAC
E2_S27_NC004162.2           GCGACAGACGGGACGCTGAAAATCCAGGTCTCCTTGCAAATTGGAATAGGGACGGATGAT
E2_99659_KJ451624.1         GCGACAGACGGGACGTTGAAAATCCAGGTTTCCTTGCAAATCGGAATAAAGACGGATGAT
                            **.**.*****.*** ************ ** *****.** **.***..***.** **

E2_181/25_L37661.3          AGCCATGATTGGACCAAGCTGCGTTACATGGACAATCATATGCCAGCAGACGCAGAGAGG
E2_IbH35_HM045786.1         AGCCACGATTGGACCAAGCTGCGCTATATGGATAGCCATACGCCAGCGGACGCGGAGCGA
E2_LR2006_KT449801.1        AGCCACGATTGGACCAAGCTGCGTTATATGGACAACCACATGCCAGCAGACGCAGAGAGG
E2_SL15649_GU189061.1       AGCCACGATTGGACCAAGCTGCGTTATATGGACAACCACATGCCAGCAGACGCAGAGAGG
E2_S27_NC004162.2           AGCCATGATTGGACCAAGCTGCGTTACATGGACAATCACATACCAGCAGACGCAGGGAGG
E2_99659_KJ451624.1         AGCCATGATTGGACCAAGCTGCGTTATATGGACAATCACATGCCAGCAGACGCAGAGCGG
                            ***** ***************** ** ***** *. ** * .*****.*****.*.*.*.
```

FIG. 15 (Cont'd)

```
E2_181/25_L37661.3          GCCAGGCTATTTGTAAGAACGTCAGCACCGTGCACGATTACTGGAACAATGGGACACTTC
E2_IbH35_HM045786.1         GCCGGATTGCTTGTAAGGACTTCAGCACCGTGCACGATCACCGGGACCATGGGACACTTT
E2_LR2006_KT449801.1        GCCGGGCTATTTGTAAGAACATCAGCACCGTGTACGATTACTGGAACAATGGGACACTTC
E2_SL15649_GU189061.1       GCCGGGCTATTTGTAAGAACATCAGCACCGTGTACGATTACTGGAACAATGGGACACTTC
E2_S27_NC004162.2           GCCGGGCTATTTGTAAGAACATCAGCACCATGCACGATTACTGGAACAATGGGACACTTC
E2_99659_KJ451624.1         GCCGGGCTATTTGTAAGAACGTCAGCACCGTGCACGATTACTGGAACAATGGGACACTTC
                            ** .*. *. ********** .** ********* ** ** **.**.**********

E2_181/25_L37661.3          ATCCTGGCCCCGATGTCCGAAAGGAGAAACTCTGACGGTGGGATTCACTGACGGTAGGAAG
E2_IbH35_HM045786.1         ATTCTGGCCCCGATGCCCGAAAGGAGAGACGCTGACAGTGGGATTTACGGACAGCAGAAAG
E2_LR2006_KT449801.1        ATCCTGGCCCCGATGTCCAAAAGGGGAAACTCTGACGGTGGGATTCACTGACAGTAGGAAG
E2_SL15649_GU189061.1       ATCCTGGCCCCGATGTCCAAAAGGGGAAACTCTGACGGTGGGATTCACTGACAGTAGGAAG
E2_S27_NC004162.2           ATCCTGGCCCCGATGTCCGAAAGGAGAAACTCTGACGGTGGGATTCACTGACAGTAGGAAG
E2_99659_KJ451624.1         ATTCTGGCCCCGATGTCCGAAAGGAGAAACTCTGACGGCGGGGTTCACTGACGGTAGGAAG
                            ** ** ********** **.*****.**.** ******.* ***.** ** ***.* **.***

E2_181/25_L37661.3          ATCAGTCACTCATGTACGCACCCATTTCACCACGACCCTCCTGTGATAGGCCGGGAAAAA
E2_IbH35_HM045786.1         ATCAGCCACACATGCACACACCCGTTCCATCATGAACCACCTGTGATAGGTAGGGAGAGG
E2_LR2006_KT449801.1        ATTAGTCACTCATGTACGCACCCATTTCACCACGACCCTCCTGTGATAGGTCGGGAAAAA
E2_SL15649_GU189061.1       ATTAGTCATTCATGTACGCACCCATTTCACCACGACCCTCCTGTGATAGGTCGGGAAAAA
E2_S27_NC004162.2           ATTAGTCACTCATGTACGCACCCATTTCACCACGACCCTCCTGTGATAGGCCGGGAAAAA
E2_99659_KJ451624.1         ATCAGTCACTCATGTACGCACCCATTTCACCATGACCCTCCTGTGATAGGCCGGGAAAAA
                            ** ** **  :***** **.*****.** ** **  **.**:********** .****.*..

E2_181/25_L37661.3          TTTCATTCCCCGACCGCAGCACGGTAGAGAAACTACCTTGCAGCACGTACGCGCAGAGCACC
E2_IbH35_HM045786.1         TTCCACTCTCGACCACAACATGGTAAAGAGAGTTACCTTGCAGCACGTACGTGCAGAGCACC
E2_LR2006_KT449801.1        TTCCATTCCCGACCGCAGCACGGTAAAGAGGCTACCTTGCAGCACGTACGTGCAGAGCACC
E2_SL15649_GU189061.1       TTCCATTCCCGACCGCAGCACGGTAAAGAGGCTACCTTGCAGCACGTACGTGCAGAGCACC
E2_S27_NC004162.2           TTCCATTCCCGACCGCAGCACGGTAAAGAGGCTACCTTGCAGCACGTACGTGCAGAGCAAC
E2_99659_KJ451624.1         TTCCATTCCCGACCGCAGCACGGTAGGGAACTACCTTGCAGCACGTACGCGCAGAGCACC
                            ** ** ** ******.**.** ****. ..**.  ********** ********** .*
```

FIG. 15 (Contd)

```
E2_181/25_L37661.3      GCTGCAACTGCCGAGGAGATAGAGGTACATATGCCCCCAGACACCCCAGATCGCACATTG
E2_IbH35_HM045786.1     GCTGCCACTGCCGAGGAGATAGAGGTGCATATGCCCCCAGATACTCCTGACCGCACGCTG
E2_LR2006_KT449801.1    GCCGCAACTACCGAGGAGATAGAGGTACACATGCCCCCAGACACCCCCTGATCGCACATTA
E2_SL15649_GU1890061.1  GCCGCAACTACCGAGGAGATAGAGGTACACATGCCCCCAGACACCCCCTGATCGCACATTA
E2_S27_NC004162.2       GCCGCAACTGCCGAGGAGATAGAGGTACACATGCCCCCAGACACCCCCTGATCGCACATTG
E2_99659_KJ451624.1     GCTGCAACTGCCGAGGAGATAGAGGTACACATGCCCCCAGACACCCCCAGATCGCACATTA
                        ** **.****.*********.**.** ********** ** **:** ******. *.

E2_181/25_L37661.3      ATGTCACAACAGTCCGGTAAATGTAAAGATCACAGTCAATAGTCAGACGGTGCGGTACAAG
E2_IbH35_HM045786.1     ATGACGGCAGCAGTCTGGCAACGTGAAGATCACAGTTAATGGGCAGACGGTGCGGTACAAG
E2_LR2006_KT449801.1    ATGTCACAACAGTCCGGCAACGTAAAGATCACAGTCAATGGCCAGACGGTGCGGTACAAG
E2_SL15649_GU1890061.1  ATGTCACAACAGTCCGGCAACGTAAAGATCACAGTCAATGGCCCAGACGGTGCGGTACAAG
E2_S27_NC004162.2       CTGTCACAACAGTCCGGCAACGTAAAGATCACAGTCAATAGTCAGACGGTGCGGTATAAG
E2_99659_KJ451624.1     ATGTCACAACAGTCCGGCAATGTAAAGATCACAGTCAATAGTCAGACGGTGCGGTACAAG
                          .**:*.**.*****  **  **.**********  ***.* ********** ***

E2_181/25_L37661.3      TGTAATTGCGGTGACTCAAATGAAGGACTAACCACTACAGACAAAGTGATTAATAACTGC
E2_IbH35_HM045786.1     TGCAACTGCGGCGGCTCAAACGAGGGACTGACAACCACAGACAAAGTGATCAATAACTGC
E2_LR2006_KT449801.1    TGTAATTGCGGTGGCTCAAATGAAGGACTAACAACTACAGACAAAGTGATTAATAACTGC
E2_SL15649_GU1890061.1  TGTAATTGCGGTGGCTCAAATGAAGGACTAACAACTACAGACAAAGTGATTAATAACTGC
E2_S27_NC004162.2       TGTAATTGCGGTGGCTCAAATGAAGGACTAATAACTACAGATAAAGTGATTAATAACTGC
E2_99659_KJ451624.1     TGCAATTGTGGTGACTCAAGTGAAGGATTAACCACTACAGATAAAGTGATTAATAACTGC
                        ** ** ** ** *.*****. **.*** *.* .** ****** ********** **********

E2_181/25_L37661.3      AAGGTTTGATCAATGCCATGCCGCGGTCACCAATCACAAAAAATGGCAGTATAATTCCCCT
E2_IbH35_HM045786.1     AAAATTGATCAGTGCCATGCTGCAGTCACTAATCACAAGAAGTGGCAATACAACTCCCCT
E2_LR2006_KT449801.1    AAGGTTTGATCAATGTCATGCCGCGGTCACCAATCACAAAAAGTGGCAGTATAACTCCCCT
E2_SL15649_GU1890061.1  AAGGTTTGATCAATGTCATGCCGCGGTCACCAATCACAAAAAGTGGCAGTATAACTCCCCT
E2_S27_NC004162.2       AAGGTTTGATCAATGTCATGCCGCGGTCACCAATCACAAAAAGTGGCAGTATAACTCCCCT
E2_99659_KJ451624.1     AAGGTCGATCAATGCCATGCCGCGGTCACCAATCACAAAAAATGGCAGTATAATTCCCCT
                        **...* ******.** ****** **.***** ********** .**.****** .** ** ******
```

FIG. 15 (Contd)

```
E2_181/25_L37661.3      CTGGTCCCGCGTAATGCTGAACTCGGGGACCGAAAAGGAAAAGTTCACATTCCGTTCCT
E2_IbH35_HM045786.1     TTAGTCCCGCGTAACGCTGAACTCGGGGACCGTAAAGGAAAGATTCACATCCCATTCCCA
E2_LR2006_KT449801.1    CTGGTCCCGCGTAATGCTGAACTTGGGGACCGAAAAGGAAAAATTCACATCCCGTTTCCG
E2_SL15649_GU189061.1   CTGGTCCCGCGTAATGCTGAACTTGGGGACCGAAAAGGAAAAATTCACATCCCGTTTCCG
E2_S27_NC004162.2       CTGGTCCCGCGTAACGCTGAACTCGGGGACCGAAAAGGAAAAATTCACATCCCGTTTCCG
E2_99659_KJ451624.1     CTGGTCCCGCGTAATGCTGAATTCGGGGACCGGAAAGGAAAAGTTCACATTTCCATTTCCT
                          *.**********  *******  *  **********  **********..********  **.**  **

E2_181/25_L37661.3      CTGGCAAATGTGACATGCAGGGTGCCTAAGGCAAGGAACCCACCGTGACGTACGGAAAA
E2_IbH35_HM045786.1     TTGGCAAACGTGACTTGCAGAGTGCCAAAAGCAAGAAACCCCACAGTAACGTACGGAAAA
E2_LR2006_KT449801.1    CTGGCAAATGTAACATGCAGGGTGCCTAAAGCAAGGAACCCCACCGTGACGTACGGGAAA
E2_SL15649_GU189061.1   CTGGCAAATGTAACATGCAGGGTGCCTAAAGCAAGGAACCCCACCGTGACGTACGGGAAA
E2_S27_NC004162.2       CTGGCAAATGTAACATGCATGGTGCCTAAAGCAAGGAACCCCACCGTGACGTACGGGAAA
E2_99659_KJ451624.1     CTGGCAAATGTGACATGCAGGGTGCCTAAAGCAAGAAACCCCACCGTGACGTACGGAAAA
                          ********  **.**:*****  .******:**.******.**********.**.**********.***

E2_181/25_L37661.3      AACCAAGTCATCATGCTGCTGTATCCTGACCACCCAACGCTCCTGTCCTACCGGAATATG
E2_IbH35_HM045786.1     AACCAAGTCACCATGCTGCTGTATCCTGACCATCCCGACACACTCTTGTCTTATCGTAACATG
E2_LR2006_KT449801.1    AACCAAGTCATCATGCTACTGTATCCTGACCACCCAACACACTCCTGTCCTACCGGAATATG
E2_SL15649_GU189061.1   AACCAAGTCATCATGCTACTGTATCCTGACCACCCAACACACTCCTGTCCTACCGGAATATG
E2_S27_NC004162.2       AACCAAGTCATCATGCTACTGTATCCTGACCACCCAACACACTCCTGTCCTACCGGAGTATG
E2_99659_KJ451624.1     AACCAAGTCATCATGTTGCTGTATCCTGACCACCCAACGCTCCTGTCCTACAGGAATATG
                          **********  *****  *.**********  **.***.***  *****  **  .*  *.  ***

E2_181/25_L37661.3      GGAGAAGAACCAAACTATCAAGAAGAGTGGGTGACGCATAAGAAGGAGATCAGGTTAACC
E2_IbH35_HM045786.1     GGACAGGAACCAAATTACCACGAGGAGTGGGTGACACACAAGAAGGAGGTTACCTTGACC
E2_LR2006_KT449801.1    GGAGAAGAACCAAACTATCAAGAAGAGTGGGTGATGCATAAGAAGGAAGTCGTGCTAACC
E2_SL15649_GU189061.1   GGAGAAGAACCAAACTATCAAGAAGAGTGGGTGATGCATAAGAAGGAAGTCGTGCTAACC
E2_S27_NC004162.2       GGAGAAGAACCAAACTATCAAGAAGAGTGGGTGACGCACAAGAAGGAGGTCGTGCTAACC
E2_99659_KJ451624.1     GGAGAAGAACCAAACTATCAAGAAGAGTGGGTGACCGCATAAGAAGGAGATCAGGTTAACC
                          *** *.**********  **  **.**.**********  .**  **********..*.  .    *.***
```

FIG. 15 (Cont'd)

```
E2_181/25_L37661.3      GTGCCGACTGAAGGGCTCGAGGTCACGTGGGGCAACAACGAGCCGTACAAGTATTGGCCG
E2_IbH35_HM045786.1     GTGCCTACTGAGGGTCTCGAGGTCACTTGGGGCAACAACGAACCATACAAGTACTGGCCG
E2_LR2006_KT449801.1    GTGCCGACTGAAGGGCTCGAGGTCACGTGGGGCAACAACGAGCCGTATAAGTATTGGCCG
E2_SL15649_GU189061.1   GTGCCGACTGAAGGGCTCGAGGTCACGTGGGGCAACAACGAGCCGTATAAGTATTGGCCG
E2_S27_NC004162.2       GTGCCGACTGAAGGGCTCGAGGTTACGTGGGGCAACAACGAGCCGTATAAGTATTGGCCG
E2_99659_KJ451624.1     GTGCCGACTGAGGGGCTCGAGGTCACGTGGGGTAACAATGAGCCGTACAAGTATTGGCCG
                        ******  ******.**  **  ******  ******  **.**.**  ****** ******

E2_181/25_L37661.3      CAGTTATCCACACAAACGGTACAGCCCACGGCCACCCGCATGAGATAATTTTGTATTATTAT
E2_IbH35_HM045786.1     CAGATGTCTACGAACGGTACTGCTCATGGTCACCCACATGAGATAATCTTGTACTATTAT
E2_LR2006_KT449801.1    CAGTTATCTACAAACGGTACAGCCCATGGCCACCCGCATGAGATAATTCTGTATTATTAT
E2_SL15649_GU189061.1   CAGTTATCTACAAACGGTACAGCCCATGGCCACCCGCATGAGATAATTCTGTATTATTAT
E2_S27_NC004162.2       CAGTTATCTGCAAACGGTACAGCCCACGGCCACCCGCATGAGATAATCTTGTACTATTAT
E2_99659_KJ451624.1     CAGTTATCCACAAACGGTACAGCCCACGGCCACCCGCATGAGATAATTCTGTATTATTAT
                        ***:*.**  .*.**********:**  **  **  ******.**********  **** ******

E2_181/25_L37661.3      GAGCTGTACCCTACTATGACTGTGGTAGTTGTGTCAGTGGCCTCGTTCGTACTCCTGTCG
E2_IbH35_HM045786.1     GAGCTGTACCCCACTATGACTGTAATCATTGTGTCGGTGGCCTCGTTCGTGCTTCTGTCG
E2_LR2006_KT449801.1    GAGCTGTACCCCACTATGACTGTAGTAGTTGTGTCAGTGGCCACGTTCATACTCCTGTCG
E2_SL15649_GU189061.1   GAGCTGTACCCTACTATGACTGTAGTAGTTGTGTCAGTGGCCACGTTCATACTCCTGTCG
E2_S27_NC004162.2       GAGCTGTACCCTACTATGACTGTAGTAGTTGTGTCAGTGGCCTCGTTCATACTACTCCTGTCG
E2_99659_KJ451624.1     GAGCTGTACCCAACTATGACTGCGGTAGTTTTGTCAGTGGCCTCGTTCATACTCCTGTCG
                        ********** ********** .*.*.** *****.*******:******.*.** *******

E2_181/25_L37661.3      ATGGTGGGTGTGGCAGTGGGGATGTGCATGTGTGCACGACGCAGATGCATTACACCGTAC
E2_IbH35_HM045786.1     ATGGTGGGCACAGCAGTGGGGATGTGTGTGCGCACGGGCGCAGATGGCATTACACCATAT
E2_LR2006_KT449801.1    ATGGTGGGTATGGCAGCGGGGATGTGCATGTGTGCACGACGCAGATGCATCACACCGTAT
E2_SL15649_GU189061.1   ATGGTGGGTATGGCAGTGGGGATGTGCATGTGTGCACGACGCAGATGCATCACACCGTAT
E2_S27_NC004162.2       ATGGTGGGTATGGCAGTGGGGATGTGCATGTGTGCACGACGCAGATGCATCACACCATAC
E2_99659_KJ451624.1     ATGGTGGGTGTGGCAGTGGGGATGTGCATGTGTGCACGACGCAGATGCATTACACCGTAC
                        **********  .  .**** ********** .**** *****.********** ******.**
```

FIG. 15 (Cont'd)

```
E2_181/25_L37661.3      GAACTGACACCAGGAGCTACCGTCCCTTTCCTGCTTAGCCTAATATGCTGCATTAGAACA
E2_IbH35_HM045786.1     GAATTAACACCAGGAGCCACCGTTCCCTTTCTGCTCAGCCTGCTATGTTGCGTCAGAACG
E2_LR2006_KT449801.1    GAACTGACACCAGGAGCTACCGTCCCTTTCCTGCTTAGCCTAATATGCTGCATCAGAACA
E2_SL15649_GU189061.1   GAACTGACACCAGGAGCTACCGTCCCTTTCCTGCTTAGCCTAATATGCTGCATCAGAACA
E2_S27_NC004162.2       GAACTGACACCAGGAGCTACCGTCCCTTTCCTGCTTAGCCTAATATGCTGCATCAGAACA
E2_99659_KJ451624.1     GAACTGACACCAGGAGCTACCGTCCCTTTCCTGCTTAGCCTAATATGCTGCATTAGAACA
                        *** *.**********  ******  **  **  ******  ..*****  ****.* ******.

E2_181/25_L37661.3      GCTAAAGCG
E2_IbH35_HM045786.1     ACCAAGGCG
E2_LR2006_KT449801.1    GCTAAAGCG
E2_SL15649_GU189061.1   GCTAAAGCG
E2_S27_NC004162.2       GCTAAAGCG
E2_99659_KJ451624.1     GCTAAAGCG
                         *  **.***
```

FIG. 15 (Contd)

```
CLUSTAL O(1.2.1) multiple sequence alignment

E2_IbH35_HM045786.1          STKDNFNVYKATRPYLAHCPDCGEGHSCHSPIALERIRNEATDGTLKIQVSLQIGIKTDD
E2_99659_KJ451624.1          SIKDHFNVYKATRPYLAHCPDCGEGHSCHSPVALERIRNEATDGTLKIQVSLQIGIKTDD
E2_181/25_L37661.3           SIKDNFNVYKAIRPYLAHCPDCGEGHSCHSPVALERIRNEATDGTLKIQVSLQIGIKTDD
E2_S27_NC004162.2            STKDNFNVYKATRPYLAHCPDCGEGHSCHSPVALERIRNEATDGTLKIQVSLQIGIGTDD
E2_SL15649_GU189061.1        STKDNFNVYKATRPYLAHCPDCGEGHSCHSPVALERIRNEATDGTLKIQVSLQIGIKTDD
E2_LR2006_KT449801.1         STKDNFNVYKATRPYLAHCPDCGEGHSCHSPVALERIRNEATDGTLKIQVSLQIGIKTDD
                             * **.****** ********************:************************ ***

E2_IbH35_HM045786.1          SHDWTKLRYMDSHTPADAERAGLLVRTSAPCTITGTMGHFILARCPKGETLTVGFTDSRK
E2_99659_KJ451624.1          SHDWTKLRYMDNHMPADAERAGLFVRTSAPCTITGTMGHFILARCPKGETLTAGFTDGRK
E2_181/25_L37661.3           SHDWTKLRYMDNHMPADAERARLFVRTSAPCTITGTMGHFILARCPKGETLTVGFTDGRK
E2_S27_NC004162.2            SHDWTKLRYMDNHIPADAGRAGLFVRTSAPCTITGTMGHFILARCPKGETLTVGFTDSRK
E2_SL15649_GU189061.1        SHDWTKLRYMDNHMPADAERAGLFVRTSAPCTITGTMGHFILARCPKGETLTVGFTDSRK
E2_LR2006_KT449801.1         SHDWTKLRYMDNHMPADAERAGLFVRTSAPCTITGTMGHFILARCPKGETLTVGFTDSRK
                             **********.* **** ** *:*****************************.****.**

E2_IbH35_HM045786.1          ISHTCTHPFHHEPPVIGRERFHSRPQHGKELPCSTYVQSTAATAEEIEVHMPPDTPDRTL
E2_99659_KJ451624.1          ISHSCTHPFHHDPPVIGREKFHSRPQHGRELPCSTYAQSTAATAEEIEVHMPPDTPDRTL
E2_181/25_L37661.3           ISHSCTHPFHHDPPVIGREKFHSRPQHGRELPCSTYAQSTAATAEEIEVHMPPDTPDRTL
E2_S27_NC004162.2            ISHSCTHPFHHDPPVIGREKFHSRPQHGRELPCSTYVQSNAATAEEIEVHMPPDTPDRTL
E2_SL15649_GU189061.1        ISHSCTHPFHHDPPVIGREKFHSRPQHGRELPCSTYVQSTAATTEEIEVHMPPDTPDRTL
E2_LR2006_KT449801.1         ISHSCTHPFHHDPPVIGREKFHSRPQHGKELPCSTYVQSTAATTEEIEVHMPPDTPDRTL
                             ***:*******:*******:********:*******.**.***:****************

E2_IbH35_HM045786.1          MTQQSGNVKITVNGQTVRYKCNCGGSNEGLTTTDKVINNCKIDQCHAAVTNHKKWQYNSP
E2_99659_KJ451624.1          MSQQSGNVKITVNSQTVRYKCNCGGSSEGLTTTDKVINNCKVDQCHAAVTNHKKWQYNSP
E2_181/25_L37661.3           MSQQSGNVKITVNSQTVRYKCNCGDSNEGLTTTDKVINNCKVDQCHAAVTNHKKWQYNSP
E2_S27_NC004162.2            LSQQSGNVKITVNSQTVRYKCNCGGSNEGLTTTDKVINNCKVDQCHAAVTNHKKWQYNSP
E2_SL15649_GU189061.1        MSQQSGNVKITVNGQTVRYKCNCGGSNEGLTTTDKVINNCKVDQCHAAVTNHKKWQYNSP
E2_LR2006_KT449801.1         MSQQSGNVKITVNGQTVRYKCNCGGSNEGLTTTDKVINNCKVDQCHAAVTNHKKWQYNSP
                             ::**********.********** *.*** **********:******************
```

FIG. 15 (Cont'd)

```
E2_IbH35_HM045786.1      LVPRNAELGDRKGKIHIPFPLANVTCRVPKARNPTVTYGKNQVTMLLYPDHPTLLSYRNM
E2_99659_KJ451624.1      LVPRNAEFGDRKGKVHIPFPLANVTCRVPKARNPTVTYGKNQVTMLLYPDHPTLLSYRNM
E2_181/25_L37661.3       LVPRNAELGDRKGKVHIPFPLANVTCRVPKARNPTVTYGKNQVTMLLYPDHPTLLSYRNM
E2_S27_NC_004162.2       LVPRNAELGDRKGKIHIPFPLANVTCMVPKARNPTVTYGKNQVTMLLYPDHPTLLSYRSM
E2_SL15649_GU189061.1    LVPRNAELGDRKGKIHIPFPLANVTCRVPKARNPTVTYGKNQVTMLLYPDHPTLLSYRNM
E2_LR2006_KT449801.1     LVPRNAELGDRKGKIHIPFPLANVTCRVPKARNPTVTYGKNQVTMLLYPDHPTLLSYRNM
                         ********:*********:********** ********** ********** *

E2_IbH35_HM045786.1      GQEPNYHEEWVTHKKEVTLTVPTEGLEVTWGNNEPYKYWPQMSTNGTAHGHPHEIILYYY
E2_99659_KJ451624.1      GEEPNYQEEWVTHKKEIRLTVPTEGLEVTWGNNEPYKYWPQLSTNGTAHGHPHEIILYYY
E2_181/25_L37661.3       GEEPNYQEEWVTHKKEIRLTVPTEGLEVTWGNNEPYKYWPQLSTNGTAHGHPHEIILYYY
E2_S27_NC_004162.2       GEEPNYQEEWVTHKKEVVLTVPTEGLEVTWGNNEPYKYWPQLSANGTAHGHPHEIILYYY
E2_SL15649_GU189061.1    GEEPNYQEEWVMHKKEVVLTVPTEGLEVTWGNNEPYKYWPQLSTNGTAHGHPHEIILYYY
E2_LR2006_KT449801.1     GEEPNYQEEWVMHKKEVVLTVPTEGLEVTWGNNEPYKYWPQLSTNGTAHGHPHEIILYYY
                         *:*****:***** ***** ********** ********** *:*********:*:*********

E2_IbH35_HM045786.1      ELYPTMTVIIVSVASFVLLSMVGTAVGMCVCARRRCITPYELTPGATVPFLLSLLCCVRT
E2_99659_KJ451624.1      ELYPTMTAVVLSVASFILLSMVGVAVGMCMCARRRCITPYELTPGATVPFLLSLICCIRT
E2_181/25_L37661.3       ELYPTMTVVVVSVASFVLLSMVGVAVGMCMCARRRCITPYELTPGATVPFLLSLICCIRT
E2_S27_NC_004162.2       ELYPTMTVVVVSVASFILLSMVGMAVGMCMCARRRCITPYELTPGATVPFLLSLICCIRT
E2_SL15649_GU189061.1    ELYPTMTVVVVSVATFILLSMVGMAVGMCMCARRRCITPYELTPGATVPFLLSLICCIRT
E2_LR2006_KT449801.1     ELYPTMTVVVVSVATFILLSMVGMAAGMCMCARRRCITPYELTPGATVPFLLSLICCIRT
                         ********.:.:.:***:*:*******  *.***:********************:**:**

E2_IbH35_HM045786.1      TKA
E2_99659_KJ451624.1      AKA
E2_181/25_L37661.3       AKA
E2_S27_NC_004162.2       AKA
E2_SL15649_GU189061.1    AKA
E2_LR2006_KT449801.1     AKA
                         :**
```

FIG. 15 (Contd)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 October 2016 (20.10.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/168417 A3

(51) International Patent Classification:
A61K 39/00 (2006.01) *C12N 5/12* (2006.01)
A61K 39/395 (2006.01) *C12N 15/13* (2006.01)
C07K 16/10 (2006.01)

(21) International Application Number:
PCT/US2016/027466

(22) International Filing Date:
14 April 2016 (14.04.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/147,354 14 April 2015 (14.04.2015) US

(71) Applicant: **VANDERBILT UNIVERSITY** [US/US]; 305 Kirkland Hall, 2201 West End Avenue, Nashville, TN 37240 (US).

(72) Inventors: **CROWE, James, E.**; 2101 20th Ave. South, Nashville, TN 37212 (US). **SMITH, Scott, A.**; 1140 Leatherwood Road, White Bluff, TN 37187 (US). **DERMODY, Terence**; 203 Derby Glen Lane, Brentwood, TN 37027 (US). **SILVA, Laurie**; 512 Westcrest Dr., Nashville, TN 37211 (US).

(74) Agent: **HIGHLANDER, Steven, L.**; Parker Highlander PLLC, 1120 S. Capital Of Texas Highway, Building One, Suite 200, Austin, TX 78746 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,

[Continued on next page]

(54) Title: ANTIBODY-MEDIATED NEUTRALIZATION OF CHIKUNGUNYA VIRUS

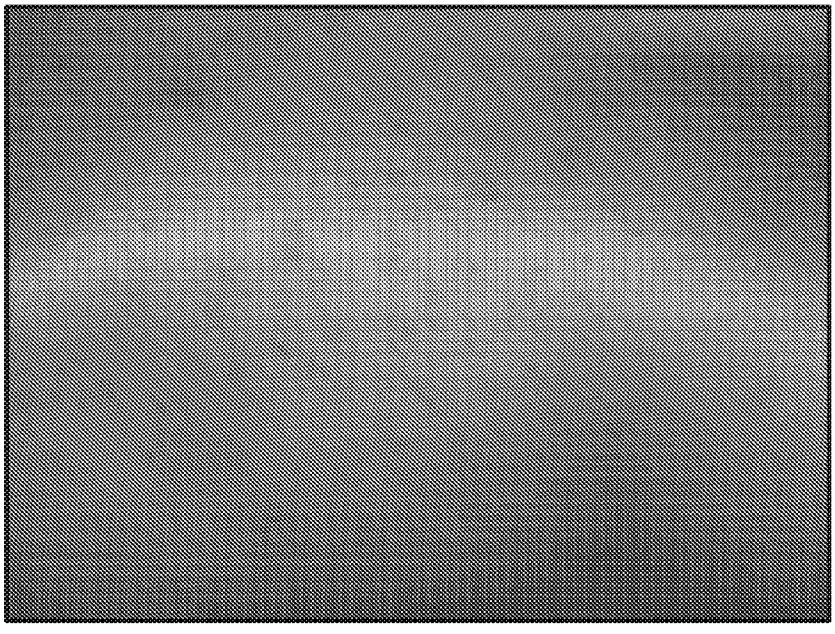


FIG. 4

(57) Abstract: The present disclosure is directed to antibodies binding to and neutralizing Chikungunya virus (CHIKV) and methods for use thereof.

WO 2016/168417 A3

LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
5 January 2017

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/027466

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/00; A61K 39/395; C07K 16/10; C12N 5/12; C12N 15/13 (2016.01)
CPC - C07K 16/1081; C07K 2317/56; C07K 2317/76; C07K 2317/565 (2016.08)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC - A61K 39/12; A61K 39/395; C07K 16/10; C12P 21/08; C12Q 1/70; G01N 33/566; G01N 33/569; G01N 33/577; G01N 33/68
CPC - A61K 39/12; C07K 16/1081; C07K 2317/21; C07K 2317/24; C07K 2317/34; C07K 2317/56; C07K 2317/565; C07K 2317/76; C07K 2317/92; C12N 2740/10023; C12N 2770/36123; C12N 2770/36134

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/147.1; 435/5; 435/7.1; 530/387.3; 530/388.3; 530/389.4 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, PubMed

Search terms used: Chikungunya OR CHIKV antibod* OR immunoglob* OR (antigen binding) E2 W3 glycoprotein%

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/010125 A1 (INTEGRAL MOLECULAR, INC. et al) 22 January 2015 (22.01.2015) entire document	1, 2, 13, 14, 17-19, 26-31, 36-42
A	US 2013/0189279 A1 (WARTER et al) 25 July 2013 (25.07.2013) entire document	1, 2, 13, 14, 17-19, 26-31, 36-42
A	CHUA et al. "Characterisation of mouse monoclonal antibodies targeting linear epitopes on Chikungunya virus E2 glycoprotein," Journal of Virological Methods, 14 October 2013 (14.10.2013), Vol. 195, Pgs. 126-133. entire document	1, 2, 13, 14, 17-19, 26-31, 36-42
A	GOH et al. "Neutralizing monoclonal antibodies to the E2 protein of chikungunya virus protects against disease in a mouse model," Clinical Immunology, 12 October 2013 (12.10.2013), Vol. 149, Iss. 3, Pgs. 487-497. entire document	1, 2, 13, 14, 17-19, 26-31, 36-42
A	SELVARAJAH et al. "A Neutralizing Monoclonal Antibody Targeting the Acid-Sensitive Region in Chikungunya Virus E2 Protects from Disease," PLoS Neglected Tropical Diseases, 12 September 2013 (12.09.2013), Vol. 7, Iss. 9, Pgs. 1-11. entire document	1, 2, 13, 14, 17-19, 26-31, 36-42

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 August 2016	07 OCT 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/027466

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 3-12, 15, 16, 20-25, 32-35, 43-46
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see Extra Sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

1, 2, 13, 14, 17 10, 26 31, 30-42 restricted to antibodies 1H12 and 4N12.

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1, 2, 13, 14, 17-19, 26-31, and 36-42 are drawn to an anti-E2 Chikungunya virus glycoprotein antibody, and methods comprising the same.

The first invention of Group I+ is restricted to an anti-E2 Chikungunya virus glycoprotein antibody, and methods comprising the same, wherein the anti-E2 Chikungunya virus glycoprotein antibody is selected to be 1H12 comprising a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:53, encoded by SEQ ID NO:2, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:103, CDR2 is selected to be SEQ ID NO:104, and CDR3 is selected to be SEQ ID NO:105; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:54, encoded by SEQ ID NO:3, the light chain further comprising light chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:187, CDR2 is selected to be SEQ ID NO:188, and CDR3 is selected to be SEQ ID NO:189. It is believed that claims 1, 2, 13, 14, 17-19, 26-31, and 36-42 read on this first named invention and thus these claims will be searched without fee to the extent that they read on 1H12 antibody and SEQ ID NOs: 2, 3, 53, 54, 103, 104, 105, 187, 188, and 189.

Applicant is invited to elect additional anti-E2 Chikungunya virus glycoprotein antibodies with specified SEQ ID NO for each heavy and light variable chains and corresponding CDR1, 2, and 3 to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be an anti-E2 Chikungunya virus glycoprotein antibody, and methods comprising the same, wherein the anti-E2 Chikungunya virus glycoprotein antibody is selected to be 2B4 comprising a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:55, encoded by SEQ ID NO:4, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:106, CDR2 is selected to be SEQ ID NO:107, and CDR3 is selected to be SEQ ID NO:108; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:56, encoded by SEQ ID NO:5, the light chain further comprising light chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:190, CDR2 is selected to be SEQ ID NO:191, and CDR3 is selected to be SEQ ID NO:192. Additional anti-E2 Chikungunya virus glycoprotein antibodies with specified SEQ ID NO for each heavy and light variable chains and corresponding CDR1, 2, and 3 will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulas do not share a significant structural element responsible for binding an E2 Chikungunya virus glycoprotein antigen, requiring the selection of alternatives for the light and heavy chain variable regions of the antibody, where "said antibody or antibody fragment is encoded by light and heavy chain variable sequences having 70%, 80%, or 90% identity to clone-paired sequences from Table 1" and "said antibody or antibody fragment comprises light and heavy chain variable sequences having 70%, 80% or 90% identity to clone-paired sequences from Table 2" and "the antibody or antibody fragment is characterized by clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively".

The Groups I+ share the technical features of a method of detecting a Chikungunya virus infection in a subject comprising: (a) contacting a sample from said subject with an antibody or antibody fragment having clone-paired heavy and light chain CDR; respectively; and (b) detecting Chikungunya virus glycoprotein E2 in said sample by binding of said antibody or antibody fragment to E2 in said sample; a method of treating a subject infected with Chikungunya Virus, or reducing the likelihood of infection of a subject at risk of contracting Chikungunya virus, comprising delivering to said subject an antibody or antibody fragment having clone paired heavy and light chain CDR sequences; a monoclonal antibody, wherein the antibody or antibody fragment is characterized by clone-paired heavy and light chain CDR sequences; hybridoma or engineered cell encoding an antibody or antibody fragment wherein the antibody or antibody fragment is characterized by clone-paired heavy and light chain CDR sequences. However, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 2015/010125 A1 to Integral Molecular, Inc. et al. discloses a method of detecting a Chikungunya virus infection in a subject (methods of detecting the presence or absence of a CHIKV antigen in a sample are provided, Para. [0014]; methods of identifying antibodies, including neutralizing antibodies, against Chikungunya virus, Abstract) comprising: (a) contacting a sample from said subject with an antibody or antibody fragment having clone-paired heavy and light chain CDR (In some embodiments, the methods comprise contacting a sample with an antibody, such as those described herein, and detecting the binding to a CHIKV antigen by the antibody, Para. [0014]; clones expressing antibodies of identical specificity, Para. [0052]); CDRs of interest in this invention are derived from donor antibody variable heavy and light chain sequences, Para. [0045]); and (b) detecting Chikungunya virus glycoprotein E2 in said sample by binding of said antibody or antibody fragment to E2 in said sample (the CHIKV antigen is the E1 protein, E2 protein, 6k protein, or E3 protein. The CHIKV antigen can also be referred to as the CHIKV protein, Para. [0073]); a method of treating a subject infected with Chikungunya Virus (Embodiments provided herein also provide methods of treating, inhibiting or ameliorating a CHIKV infection comprising administering an antibody described herein, Para. [00121]) comprising delivering to said subject an antibody or antibody fragment having clone paired heavy and light chain CDR sequences (ameliorating a CHIKV infection comprising administering an antibody described herein or a pharmaceutical composition comprising an antibody described herein, Para. [00121]; CDRs of interest in this invention are derived from donor antibody variable heavy and light chain sequences, Para. [0045]); a monoclonal antibody, wherein the antibody or antibody fragment is characterized by clone-paired heavy and light chain CDR sequences (the antibody can be a monoclonal antibody, Para. [00125]; CDRs of interest in this invention are derived from donor antibody variable heavy and light chain sequences, Para. [0045]); hybridoma or engineered cell encoding an antibody or antibody fragment wherein the antibody or antibody fragment is characterized by clone-paired heavy and light chain CDR sequences (hybridoma producing a mAb of the present invention may be cultivated in vitro, in situ or in vivo. Production of high titers of mAbs in vivo or in situ makes this the presently preferred method

of production, Para. [0050]; CDRs of interest in this invention are derived from donor antibody variable heavy and light chain sequences, Para. [0045]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

SEQUENCE LISTING

<110> Vanderbilt University

<120> ANTIBODY-MEDIATED NEUTRALIZATION OF CHIKUNGUNYA VIRUS

<130> VBLT.P0246WO

<150> US 62/147,354
<151> 2015-04-14

<160> 276

<170> PatentIn version 3.5

<210> 1
<211> 423
<212> PRT
<213> Chikungunya virus

<400> 1

Ser Thr Lys Asp Asn Phe Asn Val Tyr Lys Ala Thr Arg Pro Tyr Leu
1 5 10 15

Ala His Cys Pro Asp Cys Gly Glu Gly His Ser Cys His Ser Pro Val
20 25 30

Ala Leu Glu Arg Ile Arg Asn Glu Ala Thr Asp Gly Thr Leu Lys Ile
35 40 45

Gln Val Ser Leu Gln Ile Gly Ile Gly Thr Asp Asp Ser His Asp Trp
50 55 60

Thr Lys Leu Arg Tyr Met Asp Asn His Ile Pro Ala Asp Ala Gly Arg
65 70 75 80

Ala Gly Leu Phe Val Arg Thr Ser Ala Pro Cys Thr Ile Thr Gly Thr
85 90 95

Met Gly His Phe Ile Leu Ala Arg Cys Pro Lys Gly Glu Thr Leu Thr
100 105 110

Val Gly Phe Thr Asp Ser Arg Lys Ile Ser His Ser Cys Thr His Pro
115 120 125

Phe His His Asp Pro Pro Val Ile Gly Arg Glu Lys Phe His Ser Arg
130 135 140

Pro Gln His Gly Lys Glu Leu Pro Cys Ser Thr Tyr Val Gln Ser Asn
145 150 155 160

Ala Ala Thr Ala Glu Glu Ile Glu Val His Met Pro Pro Asp Thr Pro
165 170 175

Asp Arg Thr Leu Leu Ser Gln Gln Ser Gly Asn Val Lys Ile Thr Val
180 185 190

Asn Ser Gln Thr Val Arg Tyr Lys Cys Asn Cys Gly Gly Ser Asn Glu
195 200 205

Gly Leu Ile Thr Thr Asp Lys Val Ile Asn Asn Cys Lys Val Asp Gln
210 215 220

Cys His Ala Ala Val Thr Asn His Lys Lys Trp Gln Tyr Asn Ser Pro
225 230 235 240

Leu Val Pro Arg Asn Ala Glu Leu Gly Asp Arg Lys Gly Lys Ile His
245 250 255

Ile Pro Phe Pro Leu Ala Asn Val Thr Cys Met Val Pro Lys Ala Arg
260 265 270

Asn Pro Thr Val Thr Tyr Gly Lys Asn Gln Val Ile Met Leu Leu Tyr
275 280 285

Pro Asp His Pro Thr Leu Leu Ser Tyr Arg Ser Met Gly Glu Glu Pro
290 295 300

Asn Tyr Gln Glu Glu Trp Val Thr His Lys Lys Glu Val Val Leu Thr
305 310 315 320

Val Pro Thr Glu Gly Leu Glu Val Thr Trp Gly Asn Asn Glu Pro Tyr
325 330 335

Lys Tyr Trp Pro Gln Leu Ser Ala Asn Gly Thr Ala His Gly His Pro
340 345 350

His Glu Ile Ile Leu Tyr Tyr Tyr Glu Leu Tyr Pro Thr Met Thr Val
355 360 365

Val Val Val Ser Val Ala Ser Phe Ile Leu Leu Ser Met Val Gly Met
370 375 380

Ala Val Gly Met Cys Met Cys Ala Arg Arg Arg Cys Ile Thr Pro Tyr
385 390 395 400

Glu Leu Thr Pro Gly Ala Thr Val Pro Phe Leu Leu Ser Leu Ile Cys
405 410 415

Cys Ile Arg Thr Ala Lys Ala
420

<210> 2
<211> 378
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 2
caggtgcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cctctggtta cagctttacc agctacggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcactt acaaaggtta cacacagtat 180

gcacagaact tccagggcag agtcaccatc accacagaca cacccgcgac tacagtctat 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgcgc gagagttctt 300

tccgagactg gttatttcta ctactactac tacggtatgg acgtctgggg ccaagggacc 360

ctggtcaccg tctcctca 378

<210> 3
<211> 334
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 3
caggctgtgg tgactcagcc gccctcagtg tctggggccc cagggcagag ggtcaccatc 60

tcctgtactg ggagcagctc caacatcggg gcagattata atgtacactg gtaccagctg 120

cttccaggaa cagcccccaa actcctcatc tatggtaaca ccaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

caggctgagg atgaggctga ttattactgc cagtcctatg acagcagcct gagtgcttcg 300

gtattcggcg gagggaccaa actgaccgtc ctag 334

<210> 4
<211> 312
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 4
gcctcagtga aggtctcctg caaggcttct ggatacagtt tcactagcta ttctatcaac 60

tgggtgcgac aggcccctgg acaagggcct gagtggatgg gatggatcga caccaacact 120

gggaacccaa cctatgccca ggacttcgca ggacggtttg tcttctcctt ggacacctct 180

gtcaccacgg catatctgca gatcagcagc ctaaaggctg gggacactgc cgtttattac 240

tgtgcaacat attatgttga cctttggggg agttatcgcc aagactacta cggtatggac 300

gtctggggcc ac 312

<210> 5
<211> 333
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 5
cagtctgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60

tcttgttctg gagggagctc caacatcggg agtaatcctg taaattggta ccagatggtc 120

ccaggaacgg cccccaaact cctcctctat actaataatc agcggccctc aggggtccct 180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcaa tggactccag 240

tctgaggatg aggctgatta ttactgtgca gtatgggatg acagcctgag tggccgttgg 300

gtgttcggcg gagggaccaa ggtgaccgtc cta 333

<210> 6
<211> 411
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 6
caggtgcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgagggtc 60

tcctgcaagg cgtctggtta cacctttacc agttatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcactt acaatggtga cacaaactat 180

gcacagaagt tccagggcag agtcaccttg acaacagaga catccacgag cacagcctac 240

atggagctga ggcgcctgag atctgacgac acggccgttt actactgtgc gagagatttt 300

gaatttcccg gagattgtag tggtggcagc tgctactcca ggttcatcta ccagcacaac 360

gacatggacg tctggggcca cgggaccctg gtcaccgtct cctcagcaag c 411

<210> 7
<211> 330
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 7
caggctgtgg tgactcagcc gccctcagtg tctgcggccc caggacagaa ggtcaccatc 60

tcctgctctg gaagcagctc caacattggg aatcattatg tatcctggta ccagcacctc 120

ccgggaacag cccccaaact cctcatttat gacaattata agcgaccctc agtgattcct 180

gaccgattct ctgcctccaa gtctggcgcg tcagccaccc tgggcatcat cggactccag 240

actggggacg aggccgatta ttactgcgga acatgggata gcagcctgag tgctgtggta 300

ttcggcggag ggaccaagct gaccgtccta 330

<210> 8
<211> 381
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 8
caggtgcagc tggtgcagtc gggcccagga ctggtgaagc cttcggacac cctgtccctc 60

acctgcagtg tctcaagtga cgccctccgc agcaggagtt attactgggg ctgggtccgc 120

cagccccccg ggaagggatt ggagtggatt gggactgtct cttatagtgg gggcacctac 180

tacaacccgt ccctccagag tcgagtcacc gtgtcggtgg acacgtccaa gaaccacttc 240

tccctgaggt tgaactctgt gaccgccgca gacgcggctg tttattactg tgcgagatct 300

tatttctatg atggcagtgg ttactactac ctgagctact ttgactcctg gggccaggga 360

accctggtca ccgtctcctc a 381

<210> 9
<211> 327
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 9
caggctgtgg tgactcagga gccctcactg actgtgtccc caggagggac agtcactctc 60

acctgtgctt ccagcactgg agcagtcacc agtggtcact atccaaactg gttccagcag 120

aaacctggac aaccacccag ggccctgatt tatagcacag acaacaagca ctcctggacc 180

cctgcccggt tctcaggctc cctcctaggg gtcaaggctg ccctgacact gtcagatgta 240

cagcctgagg acgaggctga ctattactgc ctgctccatt ttggtggtgt cgtggtcttc 300

ggcggaggga ccaagctgac cgtccta 327

<210> 10
<211> 348
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 10
caggtgcagc tggtgcagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag tgtctggatt caccttcagt aactatgcca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggactg ggtggcagtt atatggtatg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaagtga acagcctgag agccgaggac acggctgtgt attactgtgc gaggggtgac 300

tacgttcttg actactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 11
<211> 324
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 11
gacattgtga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcagttgcc gggccagtca gagcattccc agctatttaa attggtatca acagaaacca 120

gggaaagccc ctaaggtcct gatctatgct acatccactt tggaagctgg ggtcccatca 180

cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcaccag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacaata cggggatatt cactttcggc 300

cctgggacca aagtggatat caaa 324

<210> 12
<211> 378
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 12
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60

tcctgcaagg cttctggagg cacttccagc acttatgcta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaggc agcatccctg tctttgctac agtaaactac 180

gcacagaagt tccagggcag actcacgatt accgcggacg aatccacgag cacagtttac 240

atggaactga gcagcctgag atctgaggac acggccgttt atttctgtgc gagcccctat 300

tgtagtagta tgaactgcta tacgaccttt tactactttg acttctgggg ccagggaacc 360

ctggtcaccg tctcctca 378

<210> 13
<211> 327
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 13
caggctgtgg tgactcagcc tgcctccgtg tttgggtttc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag tgactttggt acttataact atgtctcttg gtaccagcaa 120

cacccaggcc aagcccccaa actcatgatt tttgatgtca gtaatcggcc ctcaggggtt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240

caggctgagg acgaggcttc ttattactgc agctcctata caagcggcag cactctctac 300

ggcggaggga ccaagctgac cgtcctg 327

<210> 14
<211> 381
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 14
caggtgcagc tggtgcagtc tgggtctgag ttgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg cttctggata cagtttcact agctattcta tcaactgggt gcgacaggcc 120

cctggacaag ggcctgagtg gatgggatgg atcgacacca acactgggaa cccaacctat 180

gcccaggact tcgcaggacg gtttgtcttc tccttggaca cctctgtcac cacggcatat 240

ctgcagatca gcagcctaaa ggctggggac actgccgttt attactgtgc aacatattat 300

gttgaccttt gggggagtta tcgccaagac tactacggta tggacgtctg gggccacggg 360

accctggtca ccgtctcctc a 381

<210> 15
<211> 333
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 15
cagtctgtgg tgactcagcc accctcagtg tctgggaccc ccgggcaggg ggtcaccatc 60

tcttgttctg gagggagctc caacatcggg agtaatcctg taaattggta ccagatggtc 120

ccaggaacgg cccccaaact cctcctctat actaataatc agcggccctc aggggtccct 180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcaa tggactccag 240

tctgaggatg aggctgatta ttactgtgca gtatgggatg acagcctgag tggccgttgg 300

gtgttcggcg gagggaccaa gctgaccgtc cta 333

<210> 16
<211> 369
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 16
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg tttccggata catcctcagt aaattatccg tgcactgggt gcgacaggct 120

cctggaaaag gacttgaatg gatgggaggt tctgaacgtg aagatggcga aacagtctac 180

gcacagaagt tccagggcag aatcagcttg accgaggaca catctataga gacagcctac 240

atggagctga gcagcctgag ttctgaggac acggccgtgt attattgtgc aacaggaggc 300

ttctggagta tgattggggg aaatggagtg gactactggg gccagggaac cctggtcacc 360

gtctcctca 369

<210> 17
<211> 321
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 17
caggctgtgg tgactcagtc tccatcgtcc ctgcctgcat ctgtaggaga cagggtcacc 60

atcacttgcc gggcaagtca ggacattaga aataatttag gctggtatca gcagaaacca 120

gggaaagccc ctgagcgcct gatctatgga acctccaatt tgcagagtgg ggtcccgtca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacag cataatagtt accctcccac gttcggccgc 300

gggaccaagg tggaaatcaa a 321

<210> 18
<211> 380
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 18
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgagagtt 60

tcctgcaagg catctgggta caccttcacc agttacttta tgcactgggt gcgacaggcc 120

cctggacaag gacttgagtg gatggcgata acttatcctg gtggtggtag cccatcctac 180

gcaccgcagt tccagggcag actcaccatg accgacgaca cgtccgcgac cacagtctac 240

atggacctga gtgacctgac ttctaaagac acggccgtgt attactgtgc gagaggtgcc 300

caccgttcca ttgggacgac ccccttgac tcgtggggcc agggaaccct ggtcaccgtc 360

tcctcagcaa gcttcaaggg 380

<210> 19
<211> 375
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 19
caggtgcagc tggtgcagtc tgggggacgc gtggtccagg ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt atgtatggcg tccactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggaatg atggatctaa agaatactat 180

ggagactccg tgaagggccg attcaccatc tccagagaca attccaggaa cacgttgtat 240

ctgcaaatga acagcctgag agtcgacgac acggcagtgt atttttgtgc gagagatgga 300

attcctgacc ctgaacgcgg tgactacggg ggcttggact actggggcca gggaaccctg 360

gtcaccgtct cctca 375

<210> 20
<211> 322
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 20
cagactgtgg tgactcagtt tccatcctcc ccgtttgcat ctgtaggaga cggagtcacc 60

atcacttgcc gggcaaggca gagcattagc agttatgtta attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatttacgct acatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggata tgggacagat ttcactctca ccatcagcgg tctgcaacct 240

gaagattttg caacatacta ctgtcaacag agttacagtt ttcctcgaac gttcggccaa 300

gggaccaagg tggaaatcaa ac 322

<210> 21
<211> 381
<212> DNA
<213> Artificial sequence

<220>

<223> Synthetic oligonucleotide

<400> 21
caggtgcagc tggtgcagtc tggggctcag gtgaagaagc ctgggtcctc ggtgaaggtc 60

tcctgcaagc cctctggagg caccttcaac aacaatggga tcagttgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaggc atcgtcccga actttggaac cccaacctat 180

ggacaagact tccagggcag agtcacgatc accgcggacg aatctacgag cacagtcttc 240

ttggagctga ccagactgag atctgacgac acggccgttt atttctgtgc gcgaggtcgc 300

acggcggtga ctccgatgca attgggttta cagttctact ttgacttctg gggccgggga 360

accctggtca ccgtctcctc a 381

<210> 22
<211> 325
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 22
cagactgtgg tgactcagga gccctcactg actgtgtccc caggagggac agtcactctc 60

acctgttctg ccaacagtgg agcagtcacc agtgattact atccaaactg gttccagcag 120

aaacctggac aagcacccag ggcactgatt tatagtgcaa gcaacaaatt ctcctggacg 180

cctgcccggt tctcaggctc cctccttggg ggcaaagctg ccctgacact gtcaggtgcg 240

cagcctgagg acgaggctga gtattactgc ctggtctact ctggtgatgg tgtggttttc 300

ggcggaggga ccaagctgac cgtcc 325

<210> 23
<211> 357
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 23
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ccggggcctc agtgaaggtc 60

tcctgcaaga cttctggata tacgttcacc gacaactctg tacactgggt gcgacaggcc 120

cctggacaag ggtttgagtg gatgggacgg atcaacccta acactggtgt ctcaacttct 180

gcccagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacaacctac 240

atggagctga gcagtttgag atctgacgac acggccgtct attactgtgc gagagaggag 300

aacgatagta gtgggtatta cctttggggt cagggaaccc tggtcaccgt ctcctca 357

<210> 24
<211> 321
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 24
cagattgtgg tgactcagtc tccatcctcc ctgtttgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc acctatttaa attggtatca gcaaaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tggagagtgg ggtcccatca 180

aggttcggtg gcagtagatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagga ccccgtggac gttcggccaa 300

gggaccaagg tggacatcaa a 321

<210> 25
<211> 366
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 25
caggtgcagc tggtgcagtc tggtcctacg ctggtgaaac ccacacagac cctcacgctg 60

acctgcacct tctctgggtt ctcactcagt attagtggag tgggtgtggg ctggatccgt 120

cagcccccag gaaaggccct ggagtggctt gcactcattt attgggatga tgataagcgc 180

tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccga aaaccaggtg 240

gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacacagt 300

atgactaaag gcggggctat ctatggtcag gcctactttg aatactgggg ccagggaacc 360

ctggtc 366

<210> 26
<211> 276
<212> DNA
<213> Artificial sequence

<220>

<223> Synthetic oligonucleotide

<400> 26
ccatctcctg cactggaacc agacagtgac gttggtggtt ataactatgt ctcctggtac 60

caacaacacc caggcaaagc ccccaaactc atcatttatg atgtcactga tcggccctca 120

ggggtttcta atcgcttctc tgcctccaag tctgccaaca cggcctccct gaccatctct 180

gggctccagg ctgaggacga ggctgattat tactgcagct catatacaag cagcagcact 240

ctggttttcg gcggagggac caagctgacc gtccta 276

<210> 27
<211> 363
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 27
caggtccagc tggtacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg tttccggata caccctcact gaattatcca tgcactgggt gcgacaggct 120

cctggaaaag gcctagagtg gatgggaggt tttgagcctg aagatggtga aacaatctac 180

gcacagaagt tccagggcag agtcaccatg accgaggaca catctagaga cacagcctac 240

atggagctga gtagcctgag atctgaggac acggccgtct attactgtac aacagatcag 300

gtctactatc gttcggggag ttattctgga tatgttgact actggggcca gggaaccctg 360

gtc 363

<210> 28
<211> 363
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 28
caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc agtgaaggtc 60

tcctgcaagg cttctggacg caccttcagc agctatgtta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaggg atcatccctc tgtttggtac agcaaactac 180

gcacagaaat tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac 240

atggagctga gcagcctgag atctgacgac acggccgtct attactgtgc gaggggcgcc 300

cagctatatt acaatgatgg tagtggttac atttttgact actggggcca gggagccctg 360

gtc 363

<210> 29
<211> 390
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 29
caggtgcagc tggtgcagtc tgggcctgag gtgaagaagc ctgggacctc agtgaaggtc 60

tcctgcaagg cttctggatt cagctttatt agctctgctg tgcagtgggt gcgacaggct 120

cgtggacaac gccttgagtg gataggatgg atcgtcgttg ccagtgctaa cacaaactac 180

gcacagaagt tccgggaaag agtcaccatt actagggaca tgtccacaaa cacagcctat 240

atggaactga ccagcctgag atccgaggac acggccgttt attactgtgc ggcagagcac 300

cggtcccctt gtagtggtgg tgatagctgc tacagtctct actacggtat ggacgtctgg 360

ggccaaggga ccctggtcac cgtctcctca 390

<210> 30
<211> 354
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 30
caggtgcagc tggtgcagtc tgggggaggc ttggttccgc ctggggggtc cctgagactg 60

tcctgtacag cctctggatt caccgttagt aactatggca tgagctgggt ccgccagact 120

ccagggaagg ggctggagtg ggtctcaact attagtacta gtagtggtag aacattctac 180

gcagactccg tggagggccg gttcaccatc tccggagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agtcgaagac acggccgtat attactgtgc gaaaggcccg 300

ttcgggggcg actttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> 31
<211> 321
<212> DNA
<213> Artificial sequence

<220>

<223> Synthetic oligonucleotide

<400> 31
caggctgtgg tgactcagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttgcc atctacttag cctggtatca acagaaacct 120

ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240

gaagattttg cagtttatta ctgtcagcag cgtggcaact ggcagtacac ttttggccag 300

gggaccaaac tggagatcaa a 321

<210> 32
<211> 369
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 32
caggtgcagc tggtgcagtc tgggggaggc ctggtacagc ctggcaggtc cctgacactc 60

tcctgtgcag cctctggatt cacctttgat gtttatgcca tgcactgggt ccggcaagct 120

ccagggaagg gcttggagtg ggtcgcaggt attagttgga atagtggtag cgtaggctat 180

gcggactcta tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatta acagtctgag agctgaggac acggccttat attactgtgc aaaagcattc 300

tggttcgggg agttatcggg ttacggtatg gacgtctggg gccaagggac cctggtcacc 360

gtctcctca 369

<210> 33
<211> 330
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 33
caggctgtgg tgactcagcc tccctccgcg tccgggtttc ctggacagtc agtcaccatc 60

tcctgcactg gaaccagcag tgacgttggt agttataact atgtctcctg gtaccaacag 120

cacccaggca aagcccccaa actcataatt tatgcggtca ctaggcggcc ctcaggggtc 180

cctgagcgct tctctggctc caagtctggc aacacggcct ccctgaccgt ctctgggctc 240

caggctgagg atgaggctga ttattactgc acctcatatg caggcaacaa caaggatgtc 300

ttcggaactg ggaccaaggt caccgtccta 330

<210> 34
<211> 357
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 34
caggtgcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cagctttaac atctatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtaa cacaaactat 180

gcacagaaac tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaccactt 300

tgggggggaat tttactatga tatctggggc caagggaccc tggtcaccgt ctcctca 357

<210> 35
<211> 324
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 35
caggctgtgg tgactcagtc tccaggcacc ctgtccttgt ctccagggga aagagccacc 60

ctctcttgca gggccagtca gagtgttagc agcgggtact cagcctggta ccagcagaaa 120

cctggccagg ctcccaggct cctcatctat ggtgcatcca aaagggccgc tggcatccca 180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240

cctgaagatt ttgcagtgta ttactgtcag ctgtttgcta cctcacctcc gcccttcggc 300

caagggacac gactggagat taaa 324

<210> 36
<211> 399
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 36
caggtgcagc tggtgcagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt aattatgtta tggagtgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagcaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgttgtat 240

ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagatcagag 300

tgggagtctt cctatggttc ggggaattat tatacagatt acttctacta ctacgctatg 360

gacgtctggg gcccagggac cctggtcacc gtctcctca 399

<210> 37
<211> 336
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 37
caggctgtgg tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctaatca gagcctcctg cgtggtatta gatacaacta tttggattgg 120

tacctgcaga aaccagggca gtctccacag ctcctgatct atttgggttc taatcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcagcca cagattttac actgaaaatc 240

agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactcct 300

accaccttcg gccaagggac acgactggag attaaa 336

<210> 38
<211> 387
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 38
caggtgcagc tggaggagtc tggtcctacg ctggtgaaac ccacacagac cctcacgctg 60

acctgttcct tctctgggtt ctcactcacc actactggag tgactgtggg ctggatccgt 120

cagcccccag gaaaggcctt ggagtggctt gcactcattt attgggatga tgataagcgc 180

tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg 240

gtccttacca tgaccaacat ggaccctgtg gacactgcca catattactg tgcgcactcc 300

accggctact atgatagtag tggctatcga ggggcccttg atgcttttgc tgtctggggc 360

caagggaccc tggtcaccgt ctcctca 387

<210> 39
<211> 339
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 39
cagattgtgg tgactcagtt tccagactcc ccggctgtgt ctttgggcga gagggccacc 60

atcaactgca agtccagcca gagtgtttta taccactcca acaataaaaa ctacttagct 120

tggtaccagc agaaaccagg acagcctcct aacctgctca tttactgggc atctgcccga 180

caatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240

atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaata ttatagtact 300

ccgtacactt ttggccaggg gaccaagctg gagatcaaa 339

<210> 40
<211> 381
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 40
caggtgcagc tggtgcagtc gggcccagga ctggtgaagc cttcggacac cctgtccctc 60

acctgcagtg tctcaagtga cgccctccgc agcaggagtt attactgggg ctgggtccgc 120

cagccccccg ggaagggatt ggagtggatt gggactgtct cttatagtgg gggcacctac 180

tacaacccgt ccctccagag tcgagtcacc gtgtcggtgg acacgtccaa gaaccacttc 240

tccctgaggt tgaactctgt gaccgccgca gacgcggctg tttattactg tgcgagatct 300

tatttctatg atggcagtgg ttactactac ctgagctact ttgactcctg gggccaggga 360

accctggtca ccgtctcctc a 381

<210> 41
<211> 327
<212> DNA
<213> Artificial sequence

<220>

<223> Synthetic oligonucleotide

<400> 41
caggctgtgg tgactcagga gccctcactg actgtgtccc caggagggac agtcactctc 60

acctgtgctt ccagcactgg agcagtcacc agtggtcact atccaaactg gttccagcag 120

aaacctggac aaccacccag ggccctgatt tatagcacag acaacaagca ctcctggacc 180

cctgcccggt tctcaggctc cctcctaggg gtcaaggctg ccctgacact gtcagatgta 240

cagcctgagg acgaggctga ctattactgc ctgctccatt ttggtggtgt cgtggtcttc 300

ggcggaggga ccaagctgac cgtccta 327

<210> 42
<211> 375
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 42
caggtgcagc tggtgcagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgttcaa cgtctggatt caccttcagg atgtatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggccgtt atttttaacg atggagttaa gaaatattat 180

ggagacgccg tgaagggccg attcaccgtc tccagagaca attccaggaa caccctgtat 240

ctggaaatga aaagcctgag agtcgacgac acggctgcct actactgtgc gagagacggg 300

attcctgacc ccgaacgcgg tgactacggg ggcttggact actggggcca gggaaccctg 360

gtcaccgtct cctca 375

<210> 43
<211> 322
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 43
cagactgtgg tgactcagtc tccatcctcc ctgtctgcat ctgtaggaga cacagtcacc 60

atcacttgcc gggcaagtca gagcattacc agttatttaa actggtatca gcagaaacca 120

ggaaaagccc caaagctcct catctatgct acatccagtt tgcaaagtgg gctcccctca 180

aggttcagtg gcagtggcta tgggacagaa ttcactctca ccatcagtgg tctgcaacct 240

gaagattttg caacatacta ctgtcaacag agttacagtt ttcctcgaac gttcggccaa 300

gggaccaagg tggaaatgga ta 322

<210> 44
<211> 372
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 44
caggtgcagc tggtgcagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60

tcctgtgcaa cctctggatt catctttgat gattatgcca tgtactgggt ccggcaagct 120

ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggaaa catagcctat 180

gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ttggaaatga acagtctgag agctgaggac acggccttgt attactgtgt aaaagatctt 300

tacgggtacg atattttgac tggtaatgga tatgattact ggggccaggg aaccctggtc 360

accgtctcct ca 372

<210> 45
<211> 337
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 45
caggctgtgg tgactcagtc ttcactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctcctg caaagtaatg gatacaacta tttggattgg 120

tacctgcaga agccagggca gtctccacag ctcctgatct atttgggttc taatcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240

agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactcct 300

ccgacgttcg gccaagggac caaggtggaa atcaaaa 337

<210> 46
<211> 390
<212> DNA
<213> Artificial sequence

<220>

<223> Synthetic oligonucleotide

<400> 46
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60

ccctgcaagg cttctggaga caccctcagt tactacggaa tcacttgggt gcgacgggcc 120

cctggacaag ggcttgagtg gatgggacag atcatccctt tctttgctac aacaatctcc 180

gcacagaagt tccagggcag actcaccatg accgcggaag aatccacgag cactggctac 240

atggagcgca cattttacat ggacttgagt agccttagac ctgaggacac ggccgtatac 300

tactgtgcgg ggggctacta tggttcgggg agttcgggcg actacggttt ggacgtctgg 360

ggccaaggga ccctggtcac cgtctcctca 390

<210> 47
<211> 336
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 47
caggctgtgg tgactcagcc gccctcagtg tctggggccc cagggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacatcggg gcaggttatg atgtaaactg gtaccagcag 120

cttccaggaa cagcccccaa actcctcatc tatggtaaca acaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

caggctgagg atgaggctga ttattactgc cagtcctatg acagcagcct gagtggttcg 300

ggagtcttcg gaactgggac cgaggtcacc gtccta 336

<210> 48
<211> 384
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 48
caggtgcagc tggtgcagtc gggcccagga ctggtgaagc cttcggagac cctgtccctg 60

acgtgcgctg tttctggtga ctccatcggc agtagaagtt tctactgggg ctggatccgc 120

cagcccccag ggaaggggct ggagtggatt ggaagtatct attataatgg gaccacctac 180

tacaagccgt ccctcaagag tcgagtcacc atatccctag acacgtccaa gaaccagttc 240

tccctgaggc tgagctctct gaccgccaca gacacgggtg tctattactg tgcgcgggcg 300

ccaacctact gtagtccttc cagctgcgca gttcactggt acttcaatct ctggggccgt 360

ggcaccctgg tcaccgtctc ctca 384

<210> 49
<211> 354
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 49
caggtgcagc tggtgcagtc tggagctgag ctgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta catatttacc aaatatggta tcagttggct gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcagcgctt acaatgaaaa cacaaactat 180

gcagagaagt tccagggcag agtcaccttg accacagatg catccacgag cacggcctac 240

atggagctga ggaacctgag atctgacgac acggccgtat acttctgtgc gagagaagtc 300

tggttcgcgg agtatattta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> 50
<211> 300
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 50
caggctgtgg tgactcagga gccctcactg actgtgtccc caggagggac agtcactctc 60

acctgttctg ccaacagtgg agcagtcacc agtgattact atccaaactg gttccagcag 120

aaacctggac aagcacccag ggcactgatt tatagtgcaa gcaacaaatt ctcctggacg 180

cctgcccggt tctcaggctc cctccttggg ggcaaagctg ccctgacact gtcaggtgcg 240

cagcctgagg acgaggctga gtattactgc ctggtctact ctggtgatgg tgtggttttc 300

<210> 51
<211> 331
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 51
cagtctgtgg tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag tgacgttggt gcttataact atgtctcctg gtaccaacaa 120

cacccaggca aagcccccaa actcgtgatt tatgatgtcg ctaatcggcc ctcagggatt 180

tctgaccgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240

caggctgagg acgaggctga ttattactgc ggctcatata ccagcgacgt ctcgccggtt 300

ttcagcgggg ggaccaagct gaccgtcctc a 331

<210> 52
<211> 399
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic oligonucleotide

<400> 52
caggtgcagc tggtgcagtc tgggtctgag ttgaagaagc ctggggcctc agtgaagctt 60

tcctgcaagg cttctggata caccttcaca agtcatccta tgaattgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcaacacca agactgggaa cctaacttat 180

gcccagggct tcacaggacg gtttgtcttc tccttggaca cctctgtcag gacggcgtat 240

ctgcagatca gcggcctaaa ggctgaggac actgccattt attactgtgc gagagatgag 300

tatagtggct acgattcggt aggggtgttc cgtggttctt ttgacgactt ctacggtatg 360

gacgtctggg gccaagggac cctggtcacc gtctcctca 399

<210> 53
<211> 126
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 53

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Trp Ile Ser Thr Tyr Lys Gly Tyr Thr Gln Tyr Ala Gln Asn Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Thr Asp Thr Pro Ala Thr Thr Val Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Leu Ser Glu Thr Gly Tyr Phe Tyr Tyr Tyr Tyr Tyr Gly
100 105 110

Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 54
<211> 111
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 54

Gln Ala Val Val Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Asp
20 25 30

Tyr Asn Val His Trp Tyr Gln Leu Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asn Thr Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95

Leu Ser Ala Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 55
<211> 119
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 55

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Ser Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Pro Glu Trp Met
35 40 45

Gly Trp Ile Asp Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Asp Phe
50 55 60

Ala Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Thr Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Gly Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Tyr Tyr Val Asp Leu Trp Gly Ser Tyr Arg Gln Asp Tyr Tyr
100 105 110

Gly Met Asp Val Trp Gly His
115

<210> 56
<211> 111
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 56

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln

1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Gly Ser Ser Asn Ile Gly Ser Asn
20 25 30

Pro Val Asn Trp Tyr Gln Met Val Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Leu Tyr Thr Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Asn Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Val Trp Asp Asp Ser Leu
85 90 95

Ser Gly Arg Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 57
<211> 137
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 57

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Arg Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Thr Tyr Asn Gly Asp Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Thr Glu Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Phe Glu Phe Pro Gly Asp Cys Ser Gly Gly Ser Cys Tyr
100 105 110

Ser Arg Phe Ile Tyr Gln His Asn Asp Met Asp Val Trp Gly His Gly
115 120 125

Thr Leu Val Thr Val Ser Ser Ala Ser
130 135

<210> 58
<211> 110
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 58

Gln Ala Val Val Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
1 5 10 15

Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn His
20 25 30

Tyr Val Ser Trp Tyr Gln His Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Asp Asn Tyr Lys Arg Pro Ser Val Ile Pro Asp Arg Phe Ser
50 55 60

Ala Ser Lys Ser Gly Ala Ser Ala Thr Leu Gly Ile Ile Gly Leu Gln
65 70 75 80

Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu
85 90 95

Ser Ala Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 59
<211> 127
<212> PRT

<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 59

Gln Val Gln Leu Val Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Asp
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Ser Ser Asp Ala Leu Arg Ser Arg
20 25 30

Ser Tyr Tyr Trp Gly Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Thr Val Ser Tyr Ser Gly Gly Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Gln Ser Arg Val Thr Val Ser Val Asp Thr Ser Lys Asn His Phe
65 70 75 80

Ser Leu Arg Leu Asn Ser Val Thr Ala Ala Asp Ala Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Ser Tyr Phe Tyr Asp Gly Ser Gly Tyr Tyr Tyr Leu Ser
100 105 110

Tyr Phe Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 60
<211> 109
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 60

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Ala Ser Ser Thr Gly Ala Val Thr Ser Gly
20 25 30

His Tyr Pro Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Arg Ala
35 40 45

Leu Ile Tyr Ser Thr Asp Asn Lys His Ser Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Val Lys Ala Ala Leu Thr Leu Ser Asp Val
65 70 75 80

Gln Pro Glu Asp Glu Ala Asp Tyr Tyr Cys Leu Leu His Phe Gly Gly
85 90 95

Val Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 61
<211> 116
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 61

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Val Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asp Tyr Val Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 62
<211> 108
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 62

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

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Ser Ile Pro Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
35 40 45

Tyr Ala Thr Ser Thr Leu Glu Ala Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Asn Thr Gly Ile
85 90 95

Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 63
<211> 126
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 63

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Ser Ser Thr Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ser Ile Pro Val Phe Ala Thr Val Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Leu Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ser Pro Tyr Cys Ser Ser Met Asn Cys Tyr Thr Thr Phe Tyr Tyr
100 105 110

Phe Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 64
<211> 109
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 64

Gln Ala Val Val Thr Gln Pro Ala Ser Val Phe Gly Phe Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Phe Gly Thr Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Gln Ala Pro Lys Leu
35 40 45

Met Ile Phe Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Ser Tyr Tyr Cys Ser Ser Tyr Thr Ser Gly
85 90 95

Ser Thr Leu Tyr Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 65
<211> 127
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 65

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Ser Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Pro Glu Trp Met
35 40 45

Gly Trp Ile Asp Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Asp Phe
50 55 60

Ala Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Thr Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Gly Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Tyr Tyr Val Asp Leu Trp Gly Ser Tyr Arg Gln Asp Tyr Tyr
100 105 110

Gly Met Asp Val Trp Gly His Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 66
<211> 111
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 66

Gln Ser Val Val Thr Gln Pro Pro Ser Val Ser Gly Thr Pro Gly Gln
1 5 10 15

Gly Val Thr Ile Ser Cys Ser Gly Gly Ser Ser Asn Ile Gly Ser Asn
20 25 30

Pro Val Asn Trp Tyr Gln Met Val Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Leu Tyr Thr Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Asn Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Val Trp Asp Asp Ser Leu
85 90 95

Ser Gly Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 67
<211> 123
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 67

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Val Ser Gly Tyr Ile Leu Ser Lys Leu
20 25 30

Ser Val His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Gly Ser Glu Arg Glu Asp Gly Glu Thr Val Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Ile Ser Leu Thr Glu Asp Thr Ser Ile Glu Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Ser Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Gly Phe Trp Ser Met Ile Gly Gly Asn Gly Val Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 68
<211> 107
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 68

Gln Ala Val Val Thr Gln Ser Pro Ser Ser Leu Pro Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Asn
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Glu Arg Leu Ile
35 40 45

Tyr Gly Thr Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Pro
85 90 95

Thr Phe Gly Arg Gly Thr Lys Val Glu Ile Lys
100 105

<210> 69
<211> 126

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 69

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Arg Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Phe Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Ala Ile Thr Tyr Pro Gly Gly Gly Ser Pro Ser Tyr Ala Pro Gln Phe
50 55 60

Gln Gly Arg Leu Thr Met Thr Asp Asp Thr Ser Ala Thr Thr Val Tyr
65 70 75 80

Met Asp Leu Ser Asp Leu Thr Ser Lys Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ala His Arg Ser Ile Gly Thr Thr Pro Leu Asp Ser Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Phe Lys
115 120 125

<210> 70
<211> 125
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 70

Gln Val Gln Leu Val Gln Ser Gly Gly Arg Val Val Gln Ala Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Met Tyr
20 25 30

Gly Val His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Asn Asp Gly Ser Lys Glu Tyr Tyr Gly Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Val Asp Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Asp Gly Ile Pro Asp Pro Glu Arg Gly Asp Tyr Gly Gly Leu
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 71
<211> 107
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 71

Gln Thr Val Val Thr Gln Phe Pro Ser Ser Pro Phe Ala Ser Val Gly
1 5 10 15

Asp Gly Val Thr Ile Thr Cys Arg Ala Arg Gln Ser Ile Ser Ser Tyr
20 25 30

Val Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Gly Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 72
<211> 127
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 72

Gln Val Gln Leu Val Gln Ser Gly Ala Gln Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Pro Ser Gly Gly Thr Phe Asn Asn Asn
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Val Pro Asn Phe Gly Thr Pro Thr Tyr Gly Gln Asp Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Val Phe
65 70 75 80

Leu Glu Leu Thr Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Gly Arg Thr Ala Val Thr Pro Met Gln Leu Gly Leu Gln Phe
100 105 110

Tyr Phe Asp Phe Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 73
<211> 108
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 73

Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Ser Ala Asn Ser Gly Ala Val Thr Ser Asp
20 25 30

Tyr Tyr Pro Asn Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Ala
35 40 45

Leu Ile Tyr Ser Ala Ser Asn Lys Phe Ser Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Ala
65 70 75 80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Leu Val Tyr Ser Gly Asp
85 90 95

Gly Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val
100 105

<210> 74
<211> 119
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 74

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Ser Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Phe Glu Trp Met
35 40 45

Gly Arg Ile Asn Pro Asn Thr Gly Val Ser Thr Ser Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Thr Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Glu Asn Asp Ser Ser Gly Tyr Tyr Leu Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 75
<211> 107
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 75

Gln Ile Val Val Thr Gln Ser Pro Ser Ser Leu Phe Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Thr Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Gly Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105

<210> 76
<211> 122
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 76

Gln Val Gln Leu Val Gln Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Ile Ser
20 25 30

Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35 40 45

Trp Leu Ala Leu Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Ser Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Glu Asn Gln Val
65 70 75 80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala His Ser Met Thr Lys Gly Gly Ala Ile Tyr Gly Gln Ala Tyr
100 105 110

Phe Glu Tyr Trp Gly Gln Gly Thr Leu Val
115 120

<210> 77
<211> 80
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 77

Pro Ser Pro Ala Leu Glu Pro Asp Ser Asp Val Gly Gly Tyr Asn Tyr
1 5 10 15

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Ile Ile
20 25 30

Tyr Asp Val Thr Asp Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Ala
35 40 45

Ser Lys Ser Ala Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
50 55 60

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr
65 70 75 80

<210> 78
<211> 121
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 78

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Val Ser Gly Tyr Thr Leu Thr Glu Leu
20 25 30

Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Gly Phe Glu Pro Glu Asp Gly Glu Thr Ile Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Arg Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Thr Asp Gln Val Tyr Tyr Arg Ser Gly Ser Tyr Ser Gly Tyr Val
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val
115 120

<210> 79
<211> 121
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 79

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Arg Thr Phe Ser Ser Tyr
20 25 30

Val Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Leu Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ala Gln Leu Tyr Tyr Asn Asp Gly Ser Gly Tyr Ile Phe
100 105 110

Asp Tyr Trp Gly Gln Gly Ala Leu Val
115 120

<210> 80
<211> 130
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 80

Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Lys Pro Gly Thr
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Ser Phe Ile Ser Ser
20 25 30

Ala Val Gln Trp Val Arg Gln Ala Arg Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Val Ala Ser Ala Asn Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Arg Glu Arg Val Thr Ile Thr Arg Asp Met Ser Thr Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Glu His Arg Ser Pro Cys Ser Gly Gly Asp Ser Cys Tyr Ser
100 105 110

Leu Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val
115 120 125

Ser Ser
130

<210> 81
<211> 118
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 81

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Pro Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Val Ser Asn Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Thr Ser Ser Gly Arg Thr Phe Tyr Ala Asp Ser Val
50 55 60

Glu Gly Arg Phe Thr Ile Ser Gly Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Pro Phe Gly Gly Asp Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 82
<211> 107
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 82

Gln Ala Val Val Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ala Ile Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Gly Asn Trp Gln Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 83
<211> 123
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 83

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Val Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gly Ile Ser Trp Asn Ser Gly Ser Val Gly Tyr Ala Asp Ser Met
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Ile Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Ala Phe Trp Phe Gly Glu Leu Ser Gly Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 84
<211> 110
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 84

Gln Ala Val Val Thr Gln Pro Pro Ser Ala Ser Gly Phe Pro Gly Gln
1 5 10 15

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Ile Ile Tyr Ala Val Thr Arg Arg Pro Ser Gly Val Pro Glu Arg Phe

50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Val Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Thr Ser Tyr Ala Gly Asn
85 90 95

Asn Lys Asp Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 85
<211> 119
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 85

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Asn Ile Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Pro Leu Trp Gly Glu Phe Tyr Tyr Asp Ile Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 86
<211> 108
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 86

Gln Ala Val Val Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Gly
20 25 30

Tyr Ser Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Lys Arg Ala Ala Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Leu Phe Ala Thr Ser Pro
85 90 95

Pro Pro Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 87
<211> 133
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 87

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Val Met Glu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Glu Trp Glu Ser Ser Tyr Gly Ser Gly Asn Tyr Tyr Thr
100 105 110

Asp Tyr Phe Tyr Tyr Tyr Ala Met Asp Val Trp Gly Pro Gly Thr Leu
115 120 125

Val Thr Val Ser Ser
130

<210> 88
<211> 112
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 88

Gln Ala Val Val Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Asn Gln Ser Leu Leu Arg Gly
20 25 30

Ile Arg Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Ala Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Thr Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

<210> 89
<211> 129
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 89

Gln Val Gln Leu Glu Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Thr Thr Thr
20 25 30

Gly Val Thr Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35 40 45

Trp Leu Ala Leu Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Ser Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala His Ser Thr Gly Tyr Tyr Asp Ser Ser Gly Tyr Arg Gly Ala
100 105 110

Leu Asp Ala Phe Ala Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 90
<211> 113
<212> PRT

<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 90

Gln Ile Val Val Thr Gln Phe Pro Asp Ser Pro Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr His
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Asn Leu Leu Ile Tyr Trp Ala Ser Ala Arg Gln Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 91
<211> 127
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 91

Gln Val Gln Leu Val Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Asp
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Ser Ser Asp Ala Leu Arg Ser Arg
20 25 30

Ser Tyr Tyr Trp Gly Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Thr Val Ser Tyr Ser Gly Gly Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Gln Ser Arg Val Thr Val Ser Val Asp Thr Ser Lys Asn His Phe
65 70 75 80

Ser Leu Arg Leu Asn Ser Val Thr Ala Ala Asp Ala Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Ser Tyr Phe Tyr Asp Gly Ser Gly Tyr Tyr Tyr Leu Ser
100 105 110

Tyr Phe Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 92
<211> 109
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 92

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Ala Ser Ser Thr Gly Ala Val Thr Ser Gly
20 25 30

His Tyr Pro Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Arg Ala
35 40 45

Leu Ile Tyr Ser Thr Asp Asn Lys His Ser Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Val Lys Ala Ala Leu Thr Leu Ser Asp Val
65 70 75 80

Gln Pro Glu Asp Glu Ala Asp Tyr Tyr Cys Leu Leu His Phe Gly Gly
85 90 95

Val Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 93
<211> 125
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 93

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ser Thr Ser Gly Phe Thr Phe Arg Met Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Phe Asn Asp Gly Val Lys Lys Tyr Tyr Gly Asp Ala Val
50 55 60

Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr
65 70 75 80

Leu Glu Met Lys Ser Leu Arg Val Asp Asp Thr Ala Ala Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Ile Pro Asp Pro Glu Arg Gly Asp Tyr Gly Gly Leu
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 94
<211> 107
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 94

Gln Thr Val Val Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Thr Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Thr Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Thr Ser Ser Leu Gln Ser Gly Leu Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Glu Phe Thr Leu Thr Ile Ser Gly Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Met Asp
100 105

<210> 95
<211> 124
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 95

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Ile Phe Asp Asp Tyr
20 25 30

Ala Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Asn Ile Ala Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Glu Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Val Lys Asp Leu Tyr Gly Tyr Asp Ile Leu Thr Gly Asn Gly Tyr Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 96
<211> 112
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 96

Gln Ala Val Val Thr Gln Ser Ser Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Gln Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 97
<211> 130
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 97

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Pro Cys Lys Ala Ser Gly Asp Thr Leu Ser Tyr Tyr
20 25 30

Gly Ile Thr Trp Val Arg Arg Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gln Ile Ile Pro Phe Phe Ala Thr Thr Ile Ser Ala Gln Lys Phe
50 55 60

Gln Gly Arg Leu Thr Met Thr Ala Glu Glu Ser Thr Ser Thr Gly Tyr
65 70 75 80

Met Glu Arg Thr Phe Tyr Met Asp Leu Ser Ser Leu Arg Pro Glu Asp
85 90 95

Thr Ala Val Tyr Tyr Cys Ala Gly Gly Tyr Tyr Gly Ser Gly Ser Ser
100 105 110

Gly Asp Tyr Gly Leu Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val
115 120 125

Ser Ser
130

<210> 98
<211> 112
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 98

Gln Ala Val Val Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Asp Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asn Asn Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95

Leu Ser Gly Ser Gly Val Phe Gly Thr Gly Thr Glu Val Thr Val Leu
100 105 110

<210> 99
<211> 128
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 99

Gln Val Gln Leu Val Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Asp Ser Ile Gly Ser Arg
20 25 30

Ser Phe Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Ser Ile Tyr Tyr Asn Gly Thr Thr Tyr Tyr Lys Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Arg Leu Ser Ser Leu Thr Ala Thr Asp Thr Gly Val Tyr Tyr
85 90 95

Cys Ala Arg Ala Pro Thr Tyr Cys Ser Pro Ser Ser Cys Ala Val His
100 105 110

Trp Tyr Phe Asn Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 100
<211> 118
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 100

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Lys Tyr
20 25 30

Gly Ile Ser Trp Leu Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Glu Asn Thr Asn Tyr Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Thr Asp Ala Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Glu Val Trp Phe Ala Glu Tyr Ile Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 101
<211> 110
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 101

Gln Ser Val Val Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Val Ile Tyr Asp Val Ala Asn Arg Pro Ser Gly Ile Ser Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Asp
85 90 95

Val Ser Pro Val Phe Ser Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 102
<211> 133
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 102

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser His
20 25 30

Pro Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Lys Thr Gly Asn Leu Thr Tyr Ala Gln Gly Phe
50 55 60

Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Arg Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Gly Leu Lys Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Asp Glu Tyr Ser Gly Tyr Asp Ser Val Gly Val Phe Arg Gly
100 105 110

Ser Phe Asp Asp Phe Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Leu
115 120 125

Val Thr Val Ser Ser
130

<210> 103
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 103

Gly Tyr Ser Phe Thr Ser Tyr Gly
1 5

<210> 104
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 104

Ile Ser Thr Tyr Lys Gly Tyr Thr
1 5

<210> 105
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 105

Ala Arg Val Leu Ser Glu Thr Gly Tyr Phe Tyr Tyr Tyr Tyr Tyr Gly

1 5 10 15

Met Asp Val

<210> 106
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 106

Gly Tyr Ser Phe Thr Ser Tyr Ser
1 5

<210> 107
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 107

Ile Asp Thr Asn Thr Gly Asn Pro
1 5

<210> 108
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 108

Ala Thr Tyr Tyr Val Asp Leu Trp Gly Ser Tyr Arg Gln Asp Tyr Tyr
1 5 10 15

Gly Met Asp Val
20

<210> 109
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 109

Gly Tyr Thr Phe Thr Ser Tyr Gly
1 5

<210> 110
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 110

Ile Ser Thr Tyr Asn Gly Asp Thr
1 5

<210> 111
<211> 28
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 111

Ala Arg Asp Phe Glu Phe Pro Gly Asp Cys Ser Gly Gly Ser Cys Tyr
1 5 10 15

Ser Arg Phe Ile Tyr Gln His Asn Asp Met Asp Val
20 25

<210> 112
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 112

Ser Asp Ala Leu Arg Ser Arg Ser Tyr Tyr
1 5 10

<210> 113

<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 113

Val Ser Tyr Ser Gly Gly Thr
1 5

<210> 114
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 114

Ala Arg Ser Tyr Phe Tyr Asp Gly Ser Gly Tyr Tyr Tyr Leu Ser Tyr
1 5 10 15

Phe Asp Ser

<210> 115
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 115

Gly Phe Thr Phe Ser Asn Tyr Ala
1 5

<210> 116
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 116

Ile Trp Tyr Asp Gly Ser Asn Lys
1 5

<210> 117
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 117

Ala Arg Gly Asp Tyr Val Leu Asp Tyr
1 5

<210> 118
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 118

Gly Gly Thr Ser Ser Thr Tyr Ala
1 5

<210> 119
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 119

Ser Ile Pro Val Phe Ala Thr Val
1 5

<210> 120
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 120

Ala Ser Pro Tyr Cys Ser Ser Met Asn Cys Tyr Thr Thr Phe Tyr Tyr
1 5 10 15

Phe Asp Phe

<210> 121
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 121

Gly Tyr Ser Phe Thr Ser Tyr Ser
1 5

<210> 122
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 122

Ile Asp Thr Asn Thr Gly Asn Pro
1 5

<210> 123
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 123

Ala Thr Tyr Tyr Val Asp Leu Trp Gly Ser Tyr Arg Gln Asp Tyr Tyr
1 5 10 15

Gly Met Asp Val
20

<210> 124
<211> 8
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 124

Gly Tyr Ile Leu Ser Lys Leu Ser
1 5

<210> 125
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 125

Ser Glu Arg Glu Asp Gly Glu Thr
1 5

<210> 126
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 126

Ala Thr Gly Gly Phe Trp Ser Met Ile Gly Gly Asn Gly Val Asp Tyr
1 5 10 15

<210> 127
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 127

Gly Tyr Thr Phe Thr Ser Tyr Phe
1 5

<210> 128
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 128

Thr Tyr Pro Gly Gly Gly Ser Pro
1 5

<210> 129
<211> 15
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 129

Ala Arg Gly Ala His Arg Ser Ile Gly Thr Thr Pro Leu Asp Ser
1 5 10 15

<210> 130
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 130

Gly Phe Thr Phe Ser Met Tyr Gly
1 5

<210> 131
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 131

Ile Trp Asn Asp Gly Ser Lys Glu
1 5

<210> 132
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 132

Ala Arg Asp Gly Ile Pro Asp Pro Glu Arg Gly Asp Tyr Gly Gly Leu
1 5 10 15

Asp Tyr

<210> 133
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 133

Gly Gly Thr Phe Asn Asn Asn Gly
1 5

<210> 134
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 134

Ile Val Pro Asn Phe Gly Thr Pro
1 5

<210> 135
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 135

Ala Arg Gly Arg Thr Ala Val Thr Pro Met Gln Leu Gly Leu Gln Phe
1 5 10 15

Tyr Phe Asp Phe
20

<210> 136

<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 136

Gly Tyr Thr Phe Thr Asp Asn Ser
1 5

<210> 137
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 137

Ile Asn Pro Asn Thr Gly Val Ser
1 5

<210> 138
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 138

Ala Arg Glu Glu Asn Asp Ser Ser Gly Tyr Tyr Leu
1 5 10

<210> 139
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 139

Gly Phe Ser Leu Ser Ile Ser Gly Val Gly
1 5 10

<210> 140
<211> 7

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 140

Ile Tyr Trp Asp Asp Asp Lys
1 5

<210> 141
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 141

Ala His Ser Met Thr Lys Gly Gly Ala Ile Tyr Gly Gln Ala Tyr Phe
1 5 10 15

Glu Tyr

<210> 142
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 142

Gly Tyr Thr Leu Thr Glu Leu Ser
1 5

<210> 143
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 143

Phe Glu Pro Glu Asp Gly Glu Thr
1 5

<210> 144
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 144

Thr Thr Asp Gln Val Tyr Tyr Arg Ser Gly Ser Tyr Ser Gly Tyr Val
1 5 10 15

Asp Tyr

<210> 145
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 145

Gly Arg Thr Phe Ser Ser Tyr Val
1 5

<210> 146
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 146

Ile Ile Pro Leu Phe Gly Thr Ala
1 5

<210> 147
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 147

Ala Arg Gly Ala Gln Leu Tyr Tyr Asn Asp Gly Ser Gly Tyr Ile Phe
1 5 10 15

Asp Tyr

<210> 148
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 148

Gly Phe Ser Phe Ile Ser Ser Ala
1 5

<210> 149
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 149

Ile Val Val Ala Ser Ala Asn Thr
1 5

<210> 150
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 150

Ala Ala Glu His Arg Ser Pro Cys Ser Gly Gly Asp Ser Cys Tyr Ser
1 5 10 15

Leu Tyr Tyr Gly Met Asp Val
20

<210> 151
<211> 8
<212> PRT

<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 151

Gly Phe Thr Val Ser Asn Tyr Gly
1 5

<210> 152
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 152

Ile Ser Thr Ser Ser Gly Arg Thr
1 5

<210> 153
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 153

Ala Lys Gly Pro Phe Gly Gly Asp Phe Asp Tyr
1 5 10

<210> 154
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 154

Gly Phe Thr Phe Asp Val Tyr Ala
1 5

<210> 155
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 155

Ile Ser Trp Asn Ser Gly Ser Val
1 5

<210> 156
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 156

Ala Lys Ala Phe Trp Phe Gly Glu Leu Ser Gly Tyr Gly Met Asp Val
1 5 10 15

<210> 157
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 157

Gly Tyr Ser Phe Asn Ile Tyr Gly
1 5

<210> 158
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 158

Ile Ser Ala Tyr Asn Gly Asn Thr
1 5

<210> 159
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 159

Ala Arg Pro Leu Trp Gly Glu Phe Tyr Tyr Asp Ile
1 5 10

<210> 160
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 160

Gly Phe Thr Phe Ser Asn Tyr Val
1 5

<210> 161
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 161

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 162
<211> 26
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 162

Ala Arg Ser Glu Trp Glu Ser Ser Tyr Gly Ser Gly Asn Tyr Tyr Thr
1 5 10 15

Asp Tyr Phe Tyr Tyr Tyr Ala Met Asp Val
20 25

<210> 163
<211> 10

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 163

Gly Phe Ser Leu Thr Thr Thr Gly Val Thr
1 5 10

<210> 164
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 164

Ile Tyr Trp Asp Asp Asp Lys
1 5

<210> 165
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 165

Ala His Ser Thr Gly Tyr Tyr Asp Ser Ser Gly Tyr Arg Gly Ala Leu
1 5 10 15

Asp Ala Phe Ala Val
20

<210> 166
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 166

Ser Asp Ala Leu Arg Ser Arg Ser Tyr Tyr
1 5 10

<210> 167
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 167

Val Ser Tyr Ser Gly Gly Thr
1 5

<210> 168
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 168

Ala Arg Ser Tyr Phe Tyr Asp Gly Ser Gly Tyr Tyr Tyr Leu Ser Tyr
1 5 10 15

Phe Asp Ser

<210> 169
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 169

Gly Phe Thr Phe Arg Met Tyr Gly
1 5

<210> 170
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 170

Ile Phe Asn Asp Gly Val Lys Lys
1 5

<210> 171
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 171

Ala Arg Asp Gly Ile Pro Asp Pro Glu Arg Gly Asp Tyr Gly Gly Leu
1 5 10 15

Asp Tyr

<210> 172
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 172

Gly Phe Ile Phe Asp Asp Tyr Ala
1 5

<210> 173
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 173

Ile Ser Trp Asn Ser Gly Asn Ile
1 5

<210> 174
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 174

Val Lys Asp Leu Tyr Gly Tyr Asp Ile Leu Thr Gly Asn Gly Tyr Asp
1 5 10 15

Tyr

<210> 175
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 175

Gly Asp Thr Leu Ser Tyr Tyr Gly
1 5

<210> 176
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 176

Ile Ile Pro Phe Phe Ala Thr Thr
1 5

<210> 177
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 177

Thr Ala Val Tyr Tyr Cys Ala Gly Gly Tyr Tyr Gly Ser Gly Ser Ser
1 5 10 15

Gly Asp Tyr Gly Leu Asp Val
20

<210> 178
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 178

Gly Asp Ser Ile Gly Ser Arg Ser Phe Tyr
1 5 10

<210> 179
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 179

Ile Tyr Tyr Asn Gly Thr Thr
1 5

<210> 180
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 180

Ala Arg Ala Pro Thr Tyr Cys Ser Pro Ser Ser Cys Ala Val His Trp
1 5 10 15

Tyr Phe Asn Leu
20

<210> 181
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 181

Gly Tyr Ile Phe Thr Lys Tyr Gly

1 5

<210> 182
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 182

Ile Ser Ala Tyr Asn Glu Asn Thr
1 5

<210> 183
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 183

Ala Arg Glu Val Trp Phe Ala Glu Tyr Ile Tyr
1 5 10

<210> 184
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 184

Gly Tyr Thr Phe Thr Ser His Pro
1 5

<210> 185
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 185

Ile Asn Thr Lys Thr Gly Asn Leu
1 5

<210> 186
<211> 26
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 186

Ala Arg Asp Glu Tyr Ser Gly Tyr Asp Ser Val Gly Val Phe Arg Gly
1 5 10 15

Ser Phe Asp Asp Phe Tyr Gly Met Asp Val
20 25

<210> 187
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 187

Ser Ser Asn Ile Gly Ala Asp Tyr Asn
1 5

<210> 188
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 188

Gly Asn Thr
1

<210> 189
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 189

Gln Ser Tyr Asp Ser Ser Leu Ser Ala Ser Val
1 5 10

<210> 190
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 190

Ser Ser Asn Ile Gly Ser Asn Pro
1 5

<210> 191
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 191

Thr Asn Asn
1

<210> 192
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 192

Ala Val Trp Asp Asp Ser Leu Ser Gly Arg Trp Val
1 5 10

<210> 193
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 193

Ser Ser Asn Ile Gly Asn His Tyr
1 5

<210> 194
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 194

Asp Asn Tyr
1

<210> 195
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 195

Gly Thr Trp Asp Ser Ser Leu Ser Ala Val Val
1 5 10

<210> 196
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 196

Thr Gly Ala Val Thr Ser Gly His Tyr
1 5

<210> 197
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 197

Ser Thr Asp

1

<210> 198
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 198

Leu Leu His Phe Gly Gly Val Val Val
1 5

<210> 199
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 199

Gln Ser Ile Pro Ser Tyr
1 5

<210> 200
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 200

Ala Thr Ser
1

<210> 201
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 201

Gln Gln Ser Tyr Asn Thr Gly Ile Phe Thr
1 5 10

<210> 202
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 202

Ser Ser Asp Phe Gly Thr Tyr Asn Tyr
1 5

<210> 203
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 203

Asp Val Ser
1

<210> 204
<211> 13
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 204

Ser Ser Tyr Thr Ser Gly Ser Thr Leu Tyr Gly Gly Gly
1 5 10

<210> 205
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 205

Ser Ser Asn Ile Gly Ser Asn Pro
1 5

<210> 206
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 206

Thr Asn Asn
1

<210> 207
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 207

Ala Val Trp Asp Asp Ser Leu Ser Gly Arg Trp Val
1 5 10

<210> 208
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 208

Gln Asp Ile Arg Asn Asn
1 5

<210> 209
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 209

Gly Thr Ser
1

<210> 210
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 210

Leu Gln His Asn Ser Tyr Pro Pro Thr
1 5

<210> 211
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 211

Gln Ser Ile Ser Ser Tyr
1 5

<210> 212
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 212

Ala Thr Ser
1

<210> 213
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 213

Gln Gln Ser Tyr Ser Phe Pro Arg Thr
1 5

<210> 214

<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 214

Ser Gly Ala Val Thr Ser Asp Tyr Tyr
1 5

<210> 215
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 215

Ser Ala Ser
1

<210> 216
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 216

Leu Val Tyr Ser Gly Asp Gly Val Val
1 5

<210> 217
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 217

Gln Ser Ile Ser Thr Tyr
1 5

<210> 218
<211> 3

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 218

Ala Ala Ser
1

<210> 219
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 219

Gln Gln Ser Tyr Arg Thr Pro Trp Thr
1 5

<210> 220
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 220

Asp Ser Asp Val Gly Gly Tyr Asn Tyr
1 5

<210> 221
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 221

Asp Val Thr
1

<210> 222
<211> 10
<212> PRT

<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 222

Ser Ser Tyr Thr Ser Ser Ser Thr Leu Val
1 5 10

<210> 223
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 223

Gln Ser Val Ala Ile Tyr
1 5

<210> 224
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 224

Asp Ala Ser
1

<210> 225
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 225

Gln Gln Arg Gly Asn Trp Gln Tyr Thr
1 5

<210> 226
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 226

Ser Ser Asp Val Gly Ser Tyr Asn Tyr
1 5

<210> 227
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 227

Ala Val Thr
1

<210> 228
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 228

Thr Ser Tyr Ala Gly Asn Asn Lys Asp Val
1 5 10

<210> 229
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 229

Gln Ser Val Ser Ser Gly Tyr
1 5

<210> 230
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 230

Gly Ala Ser
1

<210> 231
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 231

Gln Leu Phe Ala Thr Ser Pro Pro Pro
1 5

<210> 232
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 232

Gln Ser Leu Leu Arg Gly Ile Arg Tyr Asn Tyr
1 5 10

<210> 233
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 233

Leu Gly Ser
1

<210> 234
<211> 9
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 234

Met Gln Ala Leu Gln Thr Pro Thr Thr
1 5

<210> 235
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 235

Gln Ser Val Leu Tyr His Ser Asn Asn Lys Asn Tyr
1 5 10

<210> 236
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 236

Trp Ala Ser
1

<210> 237
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 237

Gln Gln Tyr Tyr Ser Thr Pro Tyr Thr
1 5

<210> 238
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 238

Thr Gly Ala Val Thr Ser Gly His Tyr
1 5

<210> 239
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 239

Ser Thr Asp
1

<210> 240
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 240

Leu Leu His Phe Gly Gly Val Val Val
1 5

<210> 241
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 241

Gln Ser Ile Thr Ser Tyr
1 5

<210> 242
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 242

Ala Thr Ser
1

<210> 243
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 243

Gln Gln Ser Tyr Ser Phe Pro Arg Thr
1 5

<210> 244
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 244

Gln Ser Leu Leu Gln Ser Asn Gly Tyr Asn Tyr
1 5 10

<210> 245
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 245

Leu Gly Ser
1

<210> 246
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 246

Met Gln Ala Leu Gln Thr Pro Pro Thr
1 5

<210> 247
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 247

Ser Ser Asn Ile Gly Ala Gly Tyr Asp
1 5

<210> 248
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 248

Gly Asn Asn
1

<210> 249
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 249

Gln Ser Tyr Asp Ser Ser Leu Ser Gly Ser Gly Val
1 5 10

<210> 250
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 250

Ser Ser Asp Val Gly Ala Tyr Asn Tyr
1 5

<210> 251
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 251

Asp Val Ala
1

<210> 252
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 252

Gly Ser Tyr Thr Ser Asp Val Ser Pro Val
1 5 10

<210> 253
<211> 1317
<212> DNA
<213> Chikungunya virus

<400> 253
tacgaacacg taacagtgat cccgaacacg gtgggagtac cgtataagac tctagtcaac 60

agaccgggct acagccccat ggtactggag atggagctac tgtcagtcac tttggagcca 120

acgctatcgc ttgattacat cacgtgcgaa tacaaaaccg tcatcccgtc tccgtacgtg 180

aaatgctgcg gtacagcaga gtgcaaggac aaaaacctac ctgactacag ctgtaaggtc 240

ttcaccggcg tctacccatt tatgtggggc ggcgcctact gcttctgcga cgctgaaaac 300

acgcaattga gcgaagcaca tgtggagaag tccgaatcat gcaaaacaga atttgcatca 360

gcatacaggg ctcataccgc atccgcatca gctaagctcc gcgtccttta ccaaggaaat 420

aacatcactg taactgccta tgcaaacggc gaccatgccg tcacagttaa ggacgccaaa 480

ttcattgtgg ggccaatgtc ttcagcctgg acacctttg acaacaaaat cgtggtgtac 540

aaaggtgacg tttacaacat ggactacccg ccctttggcg caggaagacc aggacaattt 600

ggcgatatcc aaagtcgcac gcctgagagc aaagacgtct atgctaacac acaactggta 660

ctgcagagac cggctgcggg tacggtacac gtgccatact ctcaggcacc atctggcttt 720

aagtattggt taaaagaacg aggggcgtcg ctacagcaca cagcaccatt tggctgccaa 780

atagcaacaa acccggtaag agcgatgaac tgcgccgtag ggaacatgcc catctccatc 840

gacataccgg atgcggcctt cactagggtc gtcgacgcgc cctctttaac ggacatgtca 900

tgcgaggtac cagcctgcac ccattcctca gactttgggg gcgtcgccat tattaaatat 960

gcagtcagca agaaaggcaa gtgtgcggtg cattcgatga ccaacgccgt cactatccgg 1020

gaagctgaga tagaagttga agggaattct cagctgcaaa tctctttctc gacggccttg 1080

gccagcgccg aattccgcgt acaagtctgt tctacacaag tacactgtgc agccgagtgc 1140

caccctccga aggaccacat agtcaactac ccggcgtcac ataccaccct cggggtccag 1200

gacatttccg ctacggcgat gtcatgggtg cagaagatca cgggaggtgt gggactggtt 1260

gtcgctgttg cagcactgat tctaatcgtg gtgctatgcg tgtcgttcag caggcac 1317

<210> 254
<211> 1317
<212> DNA
<213> Chikungunya virus

<400> 254
tacgaacacg taacagtgat cccgaacacg gtgggagtac cgtataagac tctagtcaat 60

agacctggct acagccccat ggtattggag atggaactac tgtcagtcac tttggagcca 120

acactatcgc ttgattacat cacgtgcgag tacaaaaccg tcatcccgtc tccgtacgtg 180

aagtgctgcg gtacagcaga gtgcaaggac aaaaacctac ctgactacag ctgtaaggtc 240

ttcaccggcg tctacccatt tatgtggggc ggcgcctact gcttctgcga cgctgaaaac 300

acgcagttga gcgaagcaca tgtggagaag tccgaatcat gcaaaacaga atttgcatca 360

gcatacaggg ctcataccgc atctgcatca gctaagctcc gcgtccttta ccaaggaaat 420

aacatcactg taactgccta tgcaaacggc gaccatgccg tcacagttaa ggacgccaaa 480

ttcattgtgg ggccaatgtc ttcagcctgg acacctttcg acaacaaaat tgtggtgtac 540

aaaggtgacg tctataacat ggactacccg ccctttggcg caggaagacc aggacaattt 600

ggcgatatcc aaagtcgcac acctgagagt aaagacgtct atgctaatac acaactggta 660

ctgcagagac cggctgcggg tacggtacac gtgccatact ctcaggcacc atctggcttt 720

aagtattggc taaaagaacg cggggcgtca ctgcagcaca cagcaccatt tggctgccaa 780

atagcaacaa acccggtaag agcggtgaac tgcgccgtag ggaacatgcc catctccatc 840

gacataccgg aagcggcctt cactagggtc gtcgacgcgc cctctttaac ggacatgtcg 900

tgcgaggtac tagcctgcac ccattcctca gactttgggg gcgtcgccat tattaaatat 960

gcagccagca agaaaggcaa gtgtgcggtg cattcgatga ctaacgccgt cactattcgg 1020

gaagctgaga tagaagttga agggaattct cagctgcaaa tctctttctc gacggcctta 1080

gccagcgccg aattccgcgt acaagtctgt tctacacaag tacactgtgc agctgagtgc 1140

caccccccga aggaccacat agtcaactac ccggcgtcac ataccaccct cggggtccag 1200

gacatctccg ctacggcgat gtcatgggtg cagaagatca cgggaggtgt gggactggtt 1260

gttgctgttg ccgcactgat tctaatcgtg gtgctatgcg tgtcgttcag caggcac 1317

<210> 255
<211> 1317
<212> DNA
<213> Chikungunya virus

<400> 255
tacgaacacg taacagtgat cccgaacacg gtgggagtac cgtataagac tctagtcaat 60

agacctggct acagccccat ggtattggag atggaactac tgtcagtcac tttggagcca 120

acactatcgc ttgattacat cacgtgcgag tacaaaaccg tcatcccgtc tccgtacgtg 180

aagtgctgcg gtacagcaga gtgcaaggac aaaaacctac ctgactacag ctgtaaggtc 240

ttcaccggcg tctacccatt tatgtggggc ggcgcctact gcttctgcga cgctgaaaac 300

acgcagttga gcgaagcaca cgtggagaag tccgaatcat gcaaaacaga atttgcatca 360

gcatacaggg ctcataccgc atctgcatca gctaagctcc gcgtccttta ccaaggaaat 420

aacatcactg taactgccta tgcaaacggc gaccatgccg tcacagttaa ggacgccaaa 480

ttcattgtgg ggccaatgtc ttcagcctgg acacctttcg acaacaaaat tgtggtgtac 540

aaaggtgacg tctataacat ggactacccg ccctttggcg caggaagacc aggacaattt 600

ggcgatatcc aaagtcgcac acctgagagt aaagacgtct atgctaatac acaactggta 660

ctgcagagac cggctgtggg tacggtacac gtgccatact ctcaggcacc atctggcttt 720

aagtattggc taaaagaacg cggggcgtcg ctgcagcaca cagcaccatt tggctgccaa 780

atagcaacaa acccggtaag agcggtgaac tgcgccgtag ggaacatgcc catctccatc 840

gacataccgg aagcggcctt cactagggtc gtcgacgcgc cctctttaac ggacatgtcg 900

tgcgaggtac cagcctgcac ccattcctca gactttgggg gcgtcgccat tattaaatat 960

gcagccagca agaaaggcaa gtgtgcggtg cattcgatga ctaacgccgt cactattcgg 1020

gaagctgaga tagaagttga agggaattct cagctgcaaa tctctttctc gacggcctta 1080

gccagcgccg aattccgcgt acaagtctgt tctacacaag tacactgtgc agccgagtgc 1140

caccccccga aggaccacat agtcaactac ccggcgtcac ataccaccct cggggtccag 1200

gacatctccg ctacggcgat gtcatgggtg cagaagatca cgggaggtgt gggactggtt 1260

gttgctgttg ccgcactgat tctaatcgtg gtgctatgcg tgtcgttcag caggcac 1317

<210> 256
<211> 1317
<212> DNA
<213> Chikungunya virus

<400> 256
tacgaacacg taacagtgat cccgaacacg gtgggagtac cgtataagac tctagtcaac 60

agaccgggct acagccccat ggtactggag atggagcttc tgtcagtcac tttggagcca 120

acgctatcgc ttgattacat cacgtgcgag tataaaaccg tcatcccgtc tccgtacgtg 180

aaatgctgcg gtacagcaga gtgcaaggac aagagcctac ctgattacag ctgtaaggtc 240

ttcaccggcg tctacccatt catgtggggc ggcgcctact gcttctgcga cactgaaaat 300

acgcaattga gcgaagcaca tgtggagaag tccgaatcat gcaaaacaga atttgcatca 360

gcatataggg ctcataccgc atccgcatca gctaagctcc gcgtccttta ccaaggaaat 420

aatgttactg tatctgctta tgcaaacggc gatcatgccg tcacagttaa ggacgctaaa 480

ttcattgtgg ggccaatgtc ttcagcctgg acacctttg acaataaaat cgtggtgtac 540

aaaggcgacg tctacaacat ggactacccg cccttcggcg caggaagacc aggacaattt 600

ggcgacatcc aaagtcgcac gcctgagagc gaagacgtct atgctaacac acaactggta 660

ctgcagagac cgtccgcggg tacggtgcac gtgccgtact ctcaggcacc atctggcttc 720

aagtattggc taaaagaacg aggggcgtcg ctgcagcaca cagcaccatt tggctgtcaa 780

atagcaacaa acccggtaag agcgatgaac tgcgccgtag ggaacatgcc tatctccatc 840

gacataccgg acgcggcctt cactagggtc gtcgacgcgc catctttaac ggacatgtcg 900

tgtgaggtac cagcctgcac ccactcctca gactttgggg gcgtagccat cattaaatat 960

gcagccagca agaaaggcaa gtgtgcggtg cattcgatga ctaacgccgt cactattcgg 1020

gaagctgaaa tagaagtaga agggaactct cagttgcaaa tctctttttc gacggcccta 1080

gccagcgccg aattccgcgt acaagtctgt tctacacaag tacactgtgc agccgagtgc 1140

catccaccga aagaccatat agtcaattac ccggcgtcac acaccaccct cggggtccaa 1200

gacatttccg ttacggcgat gtcatgggtg cagaagatca cgggaggtgt gggactggtt 1260

gtcgctgttg cagcactgat cctaatcgtg gtgctatgcg tgtcgtttag caggcac 1317

<210> 257
<211> 1317
<212> DNA
<213> Chikungunya virus

<400> 257
tacgaacacg taacagtgat cccgaacacg gtgggagtac cgtataagac tctagtcaac 60

agaccgggct acagccccat ggtattggag atggagcttc tgtctgtcac cttggaacca 120

acgctatcgc ttgattacat cacgtgcgag tataaaaccg ttatcccgtc tccgtacgtg 180

aaatgctgcg gtacagcaga gtgtaaggac aagagcctac ctgattacag ctgtaaggtc 240

ttcaccggcg tctacccatt catgtggggc ggcgcctact gcttctgcga caccgaaaat 300

acgcaattga gcgaagcaca tgtggagaag tccgaatcat gcaaaacaga atttgcatca 360

gcatacaggg ctcataccgc atccgcatca gctaagctcc gcgtccttta ccaaggaaat 420

aatatcactg tggctgctta tgcaaacggc gaccatgccg tcacagttaa ggacgctaaa 480

ttcatagtgg ggccaatgtc ttcagcctgg acacctttcg acaataaaat cgtggtgtac 540

aaaggcgacg tctacaacat ggactacccg cccttcggcg caggaagacc aggacaattt 600

ggcgacatcc aaagtcgcac gcctgagagc gaagacgtct atgctaatac acaactggta 660

ctgcagagac cgtccgcggg tacggtgcac gtgccgtact ctcaggcacc atctggcttc 720

aagtattggc taaaagaacg aggggcgtcg ctgcagcaca cagcaccatt tggctgtcaa 780

atagcaacaa acccggtaag agcgatgaac tgcgccgtag ggaacatgcc tatctccatc 840

gacataccgg acgcggcctt taccagggtc gtcgacgcgc catctttaac ggacatgtcg 900

tgtgaggtat cagcctgcac ccattcctca gactttgggg gcgtagccat cattaaatat 960

gcagccagta agaaaggcaa gtgtgcagtg cactcgatga ctaacgccgt cactattcgg 1020

gaagctgaaa tagaagtaga agggaactct cagttgcaaa tctcttttc gacggcccta 1080

gccagcgccg aatttcgcgt acaagtctgt tctacacaag tacactgtgc agccgagtgc 1140

catccaccga aagaccatat agtcaattac ccggcgtcac acaccaccct cggggtccaa 1200

gacatttccg ctacggcgat gtcatgggtg cagaagatca cgggaggtgt gggactggtt 1260

gtcgctgttg cagcactgat cctaatcgtg gtgctatgcg tgtcgtttag caggcac 1317

<210> 258
<211> 1317
<212> DNA
<213> Chikungunya virus

<400> 258
tacgaacacg taacagtgat cccgaacacg gtgggagtac cgtataagac tcttgtcaac 60

agaccgggtt acagccccat ggtattggag atggagctac aatcggtcac cttggaacca 120

acactgtcac ttgactacat cacgtgcgag tacaaaactg tcatcccctc cccgtacgtg 180

aagtgctgtg gtacagcaga gtgcaaggac aagagcctac cagactacag ctgcaaggtc 240

tttactggag tctacccatt tatgtggggc ggcgcctact gcttttgcga cgccgaaaat 300

acgcaattga gcgaggcaca tgtagagaaa tctgaatctt gcaaaacaga gtttgcatcg 360

gcctacagag cccacaccgc atcggcgtcg gcgaagctcc gcgtccttta ccaaggaaac 420

aacattactg tagctgccta cgctaacggc gaccatgccg tcacagtaaa ggacgccaag 480

tttgtcgtgg gaccaatgtc ctccgcctgg acacctttg acaacaaaat cgtggtgtac 540

aaaggcgacg tctacaacat ggactaccca ccttttggcg caggaagacc aggacaattt 600

ggtgacattc aaagtcgtac accggaaagt aaagacgttt atgccaacac tcagttggta 660

ctacagaggc cagcagcagg cacggtacat gtaccatact ctcaggcacc atctggcttc 720

aagtattggc tgaaggaacg aggagcatcg ctacagcaca cggcaccgtt cggttgccag 780

attgcgacaa acccggtaag agctgtaaat tgcgctgtgg ggaacatacc aatttccatc 840

gacataccgg atgcggcctt tactagggtt gtcgatgcac cctctgtaac ggacatgtca 900

tgcgaagtac cagcctgcac tcactcctcc gactttgggg gcgtcgccat catcaaatat 960

acagctagca agaaaggtaa atgtgcagta cattcgatga ccaacgccgt taccattcga 1020

gaagccgacg tagaagtaga ggggaattcc cagctgcaaa tatccttctc aacagccttg 1080

gcaagcgccg agtttcgcgt gcaagtgtgc tccacacaag tacactgcgc agccgcatgc 1140

caccctccaa aggaccacat agtcaattac ccagcatcac acaccaccct tggggtccag 1200

gatatatcca caacggcaat gtcttgggtg cagaagatta cgggaggagt aggattaatt 1260

gttgctgttg ctgccttaat tttaattgtg gtgctatgcg tgtcgtttag caggcac 1317

<210> 259
<211> 439
<212> PRT
<213> Chikungunya virus

<400> 259

Tyr Glu His Val Thr Val Ile Pro Asn Thr Val Gly Val Pro Tyr Lys
1 5 10 15

Thr Leu Val Asn Arg Pro Gly Tyr Ser Pro Met Val Leu Glu Met Glu
20 25 30

Leu Gln Ser Val Thr Leu Glu Pro Thr Leu Ser Leu Asp Tyr Ile Thr
35 40 45

Cys Glu Tyr Lys Thr Val Ile Pro Ser Pro Tyr Val Lys Cys Cys Gly
50 55 60

Thr Ala Glu Cys Lys Asp Lys Ser Leu Pro Asp Tyr Ser Cys Lys Val
65 70 75 80

Phe Thr Gly Val Tyr Pro Phe Met Trp Gly Gly Ala Tyr Cys Phe Cys
85 90 95

Asp Ala Glu Asn Thr Gln Leu Ser Glu Ala His Val Glu Lys Ser Glu
100 105 110

Ser Cys Lys Thr Glu Phe Ala Ser Ala Tyr Arg Ala His Thr Ala Ser
115 120 125

Ala Ser Ala Lys Leu Arg Val Leu Tyr Gln Gly Asn Asn Ile Thr Val
130 135 140

Ala Ala Tyr Ala Asn Gly Asp His Ala Val Thr Val Lys Asp Ala Lys
145 150 155 160

Phe Val Val Gly Pro Met Ser Ser Ala Trp Thr Pro Phe Asp Asn Lys
165 170 175

Ile Val Val Tyr Lys Gly Asp Val Tyr Asn Met Asp Tyr Pro Pro Phe
180 185 190

Gly Ala Gly Arg Pro Gly Gln Phe Gly Asp Ile Gln Ser Arg Thr Pro
195 200 205

Glu Ser Lys Asp Val Tyr Ala Asn Thr Gln Leu Val Leu Gln Arg Pro
210 215 220

Ala Ala Gly Thr Val His Val Pro Tyr Ser Gln Ala Pro Ser Gly Phe
225 230 235 240

Lys Tyr Trp Leu Lys Glu Arg Gly Ala Ser Leu Gln His Thr Ala Pro
245 250 255

Phe Gly Cys Gln Ile Ala Thr Asn Pro Val Arg Ala Val Asn Cys Ala
260 265 270

Val Gly Asn Ile Pro Ile Ser Ile Asp Ile Pro Asp Ala Ala Phe Thr
275 280 285

Arg Val Val Asp Ala Pro Ser Val Thr Asp Met Ser Cys Glu Val Pro
290 295 300

Ala Cys Thr His Ser Ser Asp Phe Gly Gly Val Ala Ile Ile Lys Tyr
305 310 315 320

Thr Ala Ser Lys Lys Gly Lys Cys Ala Val His Ser Met Thr Asn Ala
325 330 335

Val Thr Ile Arg Glu Ala Asp Val Glu Val Glu Gly Asn Ser Gln Leu
340 345 350

Gln Ile Ser Phe Ser Thr Ala Leu Ala Ser Ala Glu Phe Arg Val Gln
355 360 365

Val Cys Ser Thr Gln Val His Cys Ala Ala Ala Cys His Pro Pro Lys
370 375 380

Asp His Ile Val Asn Tyr Pro Ala Ser His Thr Thr Leu Gly Val Gln
385 390 395 400

Asp Ile Ser Thr Thr Ala Met Ser Trp Val Gln Lys Ile Thr Gly Gly
405 410 415

Val Gly Leu Ile Val Ala Val Ala Ala Leu Ile Leu Ile Val Val Leu
420 425 430

Cys Val Ser Phe Ser Arg His
435

<210> 260
<211> 439
<212> PRT
<213> Chikungunya virus

<400> 260

Tyr Glu His Val Thr Val Ile Pro Asn Thr Val Gly Val Pro Tyr Lys
1 5 10 15

Thr Leu Val Asn Arg Pro Gly Tyr Ser Pro Met Val Leu Glu Met Glu
20 25 30

Leu Leu Ser Val Thr Leu Glu Pro Thr Leu Ser Leu Asp Tyr Ile Thr
35 40 45

Cys Glu Tyr Lys Thr Val Ile Pro Ser Pro Tyr Val Lys Cys Cys Gly
50 55 60

Thr Ala Glu Cys Lys Asp Lys Asn Leu Pro Asp Tyr Ser Cys Lys Val
65 70 75 80

Phe Thr Gly Val Tyr Pro Phe Met Trp Gly Gly Ala Tyr Cys Phe Cys
85 90 95

Asp Ala Glu Asn Thr Gln Leu Ser Glu Ala His Val Glu Lys Ser Glu
100 105 110

Ser Cys Lys Thr Glu Phe Ala Ser Ala Tyr Arg Ala His Thr Ala Ser
115 120 125

Ala Ser Ala Lys Leu Arg Val Leu Tyr Gln Gly Asn Asn Ile Thr Val
130 135 140

Thr Ala Tyr Ala Asn Gly Asp His Ala Val Thr Val Lys Asp Ala Lys
145 150 155 160

Phe Ile Val Gly Pro Met Ser Ser Ala Trp Thr Pro Phe Asp Asn Lys
165 170 175

Ile Val Val Tyr Lys Gly Asp Val Tyr Asn Met Asp Tyr Pro Pro Phe
180 185 190

Gly Ala Gly Arg Pro Gly Gln Phe Gly Asp Ile Gln Ser Arg Thr Pro

195 200 205

Glu Ser Lys Asp Val Tyr Ala Asn Thr Gln Leu Val Leu Gln Arg Pro
210 215 220

Ala Ala Gly Thr Val His Val Pro Tyr Ser Gln Ala Pro Ser Gly Phe
225 230 235 240

Lys Tyr Trp Leu Lys Glu Arg Gly Ala Ser Leu Gln His Thr Ala Pro
245 250 255

Phe Gly Cys Gln Ile Ala Thr Asn Pro Val Arg Ala Met Asn Cys Ala
260 265 270

Val Gly Asn Met Pro Ile Ser Ile Asp Ile Pro Asp Ala Ala Phe Thr
275 280 285

Arg Val Val Asp Ala Pro Ser Leu Thr Asp Met Ser Cys Glu Val Pro
290 295 300

Ala Cys Thr His Ser Ser Asp Phe Gly Gly Val Ala Ile Ile Lys Tyr
305 310 315 320

Ala Val Ser Lys Lys Gly Lys Cys Ala Val His Ser Met Thr Asn Ala
325 330 335

Val Thr Ile Arg Glu Ala Glu Ile Glu Val Glu Gly Asn Ser Gln Leu
340 345 350

Gln Ile Ser Phe Ser Thr Ala Leu Ala Ser Ala Glu Phe Arg Val Gln
355 360 365

Val Cys Ser Thr Gln Val His Cys Ala Ala Glu Cys His Pro Pro Lys
370 375 380

Asp His Ile Val Asn Tyr Pro Ala Ser His Thr Thr Leu Gly Val Gln
385 390 395 400

Asp Ile Ser Ala Thr Ala Met Ser Trp Val Gln Lys Ile Thr Gly Gly
405 410 415

Val Gly Leu Val Val Ala Val Ala Ala Leu Ile Leu Ile Val Val Leu
420 425 430

Cys Val Ser Phe Ser Arg His
435

<210> 261
<211> 439
<212> PRT
<213> Chikungunya virus

<400> 261

Tyr Glu His Val Thr Val Ile Pro Asn Thr Val Gly Val Pro Tyr Lys
1 5 10 15

Thr Leu Val Asn Arg Pro Gly Tyr Ser Pro Met Val Leu Glu Met Glu
20 25 30

Leu Leu Ser Val Thr Leu Glu Pro Thr Leu Ser Leu Asp Tyr Ile Thr
35 40 45

Cys Glu Tyr Lys Thr Val Ile Pro Ser Pro Tyr Val Lys Cys Cys Gly
50 55 60

Thr Ala Glu Cys Lys Asp Lys Asn Leu Pro Asp Tyr Ser Cys Lys Val
65 70 75 80

Phe Thr Gly Val Tyr Pro Phe Met Trp Gly Gly Ala Tyr Cys Phe Cys
85 90 95

Asp Ala Glu Asn Thr Gln Leu Ser Glu Ala His Val Glu Lys Ser Glu
100 105 110

Ser Cys Lys Thr Glu Phe Ala Ser Ala Tyr Arg Ala His Thr Ala Ser
115 120 125

Ala Ser Ala Lys Leu Arg Val Leu Tyr Gln Gly Asn Asn Ile Thr Val
130 135 140

Thr Ala Tyr Ala Asn Gly Asp His Ala Val Thr Val Lys Asp Ala Lys
145 150 155 160

Phe Ile Val Gly Pro Met Ser Ser Ala Trp Thr Pro Phe Asp Asn Lys
165 170 175

Ile Val Val Tyr Lys Gly Asp Val Tyr Asn Met Asp Tyr Pro Pro Phe
180 185 190

Gly Ala Gly Arg Pro Gly Gln Phe Gly Asp Ile Gln Ser Arg Thr Pro
195 200 205

Glu Ser Lys Asp Val Tyr Ala Asn Thr Gln Leu Val Leu Gln Arg Pro
210 215 220

Ala Ala Gly Thr Val His Val Pro Tyr Ser Gln Ala Pro Ser Gly Phe
225 230 235 240

Lys Tyr Trp Leu Lys Glu Arg Gly Ala Ser Leu Gln His Thr Ala Pro
245 250 255

Phe Gly Cys Gln Ile Ala Thr Asn Pro Val Arg Ala Val Asn Cys Ala
260 265 270

Val Gly Asn Met Pro Ile Ser Ile Asp Ile Pro Glu Ala Ala Phe Thr
275 280 285

Arg Val Val Asp Ala Pro Ser Leu Thr Asp Met Ser Cys Glu Val Leu
290 295 300

Ala Cys Thr His Ser Ser Asp Phe Gly Gly Val Ala Ile Ile Lys Tyr
305 310 315 320

Ala Ala Ser Lys Lys Gly Lys Cys Ala Val His Ser Met Thr Asn Ala
325 330 335

Val Thr Ile Arg Glu Ala Glu Ile Glu Val Glu Gly Asn Ser Gln Leu
340 345 350

Gln Ile Ser Phe Ser Thr Ala Leu Ala Ser Ala Glu Phe Arg Val Gln
355 360 365

Val Cys Ser Thr Gln Val His Cys Ala Ala Glu Cys His Pro Pro Lys
370 375 380

Asp His Ile Val Asn Tyr Pro Ala Ser His Thr Thr Leu Gly Val Gln
385 390 395 400

Asp Ile Ser Ala Thr Ala Met Ser Trp Val Gln Lys Ile Thr Gly Gly

405 410 415

Val Gly Leu Val Val Ala Val Ala Ala Leu Ile Leu Ile Val Val Leu
420 425 430

Cys Val Ser Phe Ser Arg His
435

<210> 262
<211> 439
<212> PRT
<213> Chikungunya virus

<400> 262

Tyr Glu His Val Thr Val Ile Pro Asn Thr Val Gly Val Pro Tyr Lys
1 5 10 15

Thr Leu Val Asn Arg Pro Gly Tyr Ser Pro Met Val Leu Glu Met Glu
20 25 30

Leu Leu Ser Val Thr Leu Glu Pro Thr Leu Ser Leu Asp Tyr Ile Thr
35 40 45

Cys Glu Tyr Lys Thr Val Ile Pro Ser Pro Tyr Val Lys Cys Cys Gly
50 55 60

Thr Ala Glu Cys Lys Asp Lys Asn Leu Pro Asp Tyr Ser Cys Lys Val
65 70 75 80

Phe Thr Gly Val Tyr Pro Phe Met Trp Gly Gly Ala Tyr Cys Phe Cys
85 90 95

Asp Ala Glu Asn Thr Gln Leu Ser Glu Ala His Val Glu Lys Ser Glu
100 105 110

Ser Cys Lys Thr Glu Phe Ala Ser Ala Tyr Arg Ala His Thr Ala Ser
115 120 125

Ala Ser Ala Lys Leu Arg Val Leu Tyr Gln Gly Asn Asn Ile Thr Val
130 135 140

Thr Ala Tyr Ala Asn Gly Asp His Ala Val Thr Val Lys Asp Ala Lys
145 150 155 160

Phe Ile Val Gly Pro Met Ser Ser Ala Trp Thr Pro Phe Asp Asn Lys
165 170 175

Ile Val Val Tyr Lys Gly Asp Val Tyr Asn Met Asp Tyr Pro Pro Phe
180 185 190

Gly Ala Gly Arg Pro Gly Gln Phe Gly Asp Ile Gln Ser Arg Thr Pro
195 200 205

Glu Ser Lys Asp Val Tyr Ala Asn Thr Gln Leu Val Leu Gln Arg Pro
210 215 220

Ala Val Gly Thr Val His Val Pro Tyr Ser Gln Ala Pro Ser Gly Phe
225 230 235 240

Lys Tyr Trp Leu Lys Glu Arg Gly Ala Ser Leu Gln His Thr Ala Pro
245 250 255

Phe Gly Cys Gln Ile Ala Thr Asn Pro Val Arg Ala Val Asn Cys Ala
260 265 270

Val Gly Asn Met Pro Ile Ser Ile Asp Ile Pro Glu Ala Ala Phe Thr
275 280 285

Arg Val Val Asp Ala Pro Ser Leu Thr Asp Met Ser Cys Glu Val Pro
290 295 300

Ala Cys Thr His Ser Ser Asp Phe Gly Gly Val Ala Ile Ile Lys Tyr
305 310 315 320

Ala Ala Ser Lys Lys Gly Lys Cys Ala Val His Ser Met Thr Asn Ala
325 330 335

Val Thr Ile Arg Glu Ala Glu Ile Glu Val Glu Gly Asn Ser Gln Leu
340 345 350

Gln Ile Ser Phe Ser Thr Ala Leu Ala Ser Ala Glu Phe Arg Val Gln
355 360 365

Val Cys Ser Thr Gln Val His Cys Ala Ala Glu Cys His Pro Pro Lys
370 375 380

Asp His Ile Val Asn Tyr Pro Ala Ser His Thr Thr Leu Gly Val Gln
385 390 395 400

Asp Ile Ser Ala Thr Ala Met Ser Trp Val Gln Lys Ile Thr Gly Gly
405 410 415

Val Gly Leu Val Val Ala Val Ala Ala Leu Ile Leu Ile Val Val Leu
420 425 430

Cys Val Ser Phe Ser Arg His
435

<210> 263
<211> 439
<212> PRT
<213> Chikungunya virus

<400> 263

Tyr Glu His Val Thr Val Ile Pro Asn Thr Val Gly Val Pro Tyr Lys
1 5 10 15

Thr Leu Val Asn Arg Pro Gly Tyr Ser Pro Met Val Leu Glu Met Glu
20 25 30

Leu Leu Ser Val Thr Leu Glu Pro Thr Leu Ser Leu Asp Tyr Ile Thr
35 40 45

Cys Glu Tyr Lys Thr Val Ile Pro Ser Pro Tyr Val Lys Cys Cys Gly
50 55 60

Thr Ala Glu Cys Lys Asp Lys Ser Leu Pro Asp Tyr Ser Cys Lys Val
65 70 75 80

Phe Thr Gly Val Tyr Pro Phe Met Trp Gly Gly Ala Tyr Cys Phe Cys
85 90 95

Asp Thr Glu Asn Thr Gln Leu Ser Glu Ala His Val Glu Lys Ser Glu
100 105 110

Ser Cys Lys Thr Glu Phe Ala Ser Ala Tyr Arg Ala His Thr Ala Ser
115 120 125

Ala Ser Ala Lys Leu Arg Val Leu Tyr Gln Gly Asn Asn Ile Thr Val
130 135 140

Ala Ala Tyr Ala Asn Gly Asp His Ala Val Thr Val Lys Asp Ala Lys
145 150 155 160

Phe Ile Val Gly Pro Met Ser Ser Ala Trp Thr Pro Phe Asp Asn Lys
165 170 175

Ile Val Val Tyr Lys Gly Asp Val Tyr Asn Met Asp Tyr Pro Pro Phe
180 185 190

Gly Ala Gly Arg Pro Gly Gln Phe Gly Asp Ile Gln Ser Arg Thr Pro
195 200 205

Glu Ser Glu Asp Val Tyr Ala Asn Thr Gln Leu Val Leu Gln Arg Pro
210 215 220

Ser Ala Gly Thr Val His Val Pro Tyr Ser Gln Ala Pro Ser Gly Phe
225 230 235 240

Lys Tyr Trp Leu Lys Glu Arg Gly Ala Ser Leu Gln His Thr Ala Pro
245 250 255

Phe Gly Cys Gln Ile Ala Thr Asn Pro Val Arg Ala Met Asn Cys Ala
260 265 270

Val Gly Asn Met Pro Ile Ser Ile Asp Ile Pro Asp Ala Ala Phe Thr
275 280 285

Arg Val Val Asp Ala Pro Ser Leu Thr Asp Met Ser Cys Glu Val Ser
290 295 300

Ala Cys Thr His Ser Ser Asp Phe Gly Gly Val Ala Ile Ile Lys Tyr
305 310 315 320

Ala Ala Ser Lys Lys Gly Lys Cys Ala Val His Ser Met Thr Asn Ala
325 330 335

Val Thr Ile Arg Glu Ala Glu Ile Glu Val Glu Gly Asn Ser Gln Leu
340 345 350

Gln Ile Ser Phe Ser Thr Ala Leu Ala Ser Ala Glu Phe Arg Val Gln
355 360 365

Val Cys Ser Thr Gln Val His Cys Ala Ala Glu Cys His Pro Pro Lys
370 375 380

Asp His Ile Val Asn Tyr Pro Ala Ser His Thr Thr Leu Gly Val Gln
385 390 395 400

Asp Ile Ser Ala Thr Ala Met Ser Trp Val Gln Lys Ile Thr Gly Gly
405 410 415

Val Gly Leu Val Val Ala Val Ala Ala Leu Ile Leu Ile Val Val Leu
420 425 430

Cys Val Ser Phe Ser Arg His
435

<210> 264
<211> 439
<212> PRT
<213> Chikungunya virus

<400> 264

Tyr Glu His Val Thr Val Ile Pro Asn Thr Val Gly Val Pro Tyr Lys
1 5 10 15

Thr Leu Val Asn Arg Pro Gly Tyr Ser Pro Met Val Leu Glu Met Glu
20 25 30

Leu Leu Ser Val Thr Leu Glu Pro Thr Leu Ser Leu Asp Tyr Ile Thr
35 40 45

Cys Glu Tyr Lys Thr Val Ile Pro Ser Pro Tyr Val Lys Cys Cys Gly
50 55 60

Thr Ala Glu Cys Lys Asp Lys Ser Leu Pro Asp Tyr Ser Cys Lys Val
65 70 75 80

Phe Thr Gly Val Tyr Pro Phe Met Trp Gly Gly Ala Tyr Cys Phe Cys
85 90 95

Asp Thr Glu Asn Thr Gln Leu Ser Glu Ala His Val Glu Lys Ser Glu
100 105 110

Ser Cys Lys Thr Glu Phe Ala Ser Ala Tyr Arg Ala His Thr Ala Ser

115 120 125

Ala Ser Ala Lys Leu Arg Val Leu Tyr Gln Gly Asn Asn Val Thr Val
130 135 140

Ser Ala Tyr Ala Asn Gly Asp His Ala Val Thr Val Lys Asp Ala Lys
145 150 155 160

Phe Ile Val Gly Pro Met Ser Ser Ala Trp Thr Pro Phe Asp Asn Lys
165 170 175

Ile Val Val Tyr Lys Gly Asp Val Tyr Asn Met Asp Tyr Pro Pro Phe
180 185 190

Gly Ala Gly Arg Pro Gly Gln Phe Gly Asp Ile Gln Ser Arg Thr Pro
195 200 205

Glu Ser Glu Asp Val Tyr Ala Asn Thr Gln Leu Val Leu Gln Arg Pro
210 215 220

Ser Ala Gly Thr Val His Val Pro Tyr Ser Gln Ala Pro Ser Gly Phe
225 230 235 240

Lys Tyr Trp Leu Lys Glu Arg Gly Ala Ser Leu Gln His Thr Ala Pro
245 250 255

Phe Gly Cys Gln Ile Ala Thr Asn Pro Val Arg Ala Met Asn Cys Ala
260 265 270

Val Gly Asn Met Pro Ile Ser Ile Asp Ile Pro Asp Ala Ala Phe Thr
275 280 285

Arg Val Val Asp Ala Pro Ser Leu Thr Asp Met Ser Cys Glu Val Pro
290 295 300

Ala Cys Thr His Ser Ser Asp Phe Gly Gly Val Ala Ile Ile Lys Tyr
305 310 315 320

Ala Ala Ser Lys Lys Gly Lys Cys Ala Val His Ser Met Thr Asn Ala
325 330 335

Val Thr Ile Arg Glu Ala Glu Ile Glu Val Glu Gly Asn Ser Gln Leu
340 345 350

Gln Ile Ser Phe Ser Thr Ala Leu Ala Ser Ala Glu Phe Arg Val Gln
355 360 365

Val Cys Ser Thr Gln Val His Cys Ala Ala Glu Cys His Pro Pro Lys
370 375 380

Asp His Ile Val Asn Tyr Pro Ala Ser His Thr Thr Leu Gly Val Gln
385 390 395 400

Asp Ile Ser Val Thr Ala Met Ser Trp Val Gln Lys Ile Thr Gly Gly
405 410 415

Val Gly Leu Val Val Ala Val Ala Ala Leu Ile Leu Ile Val Val Leu
420 425 430

Cys Val Ser Phe Ser Arg His
435

<210> 265
<211> 1269
<212> DNA
<213> Chikungunya virus

<400> 265
agtattaagg acaacttcaa tgtctataaa gccataagac cgtacctagc tcactgtccc 60

gactgtggag aagggcactc gtgccatagt cccgtagcgc tagaacgcat cagaaacgaa 120

gcgacagacg ggacgctgaa aatccaggtt tccttgcaaa tcggaataaa gacggatgat 180

agccatgatt ggaccaagct gcgttacatg gacaatcata tgccagcaga cgcagagagg 240

gccaggctat ttgtaagaac gtcagcaccg tgcacgatta ctggaacaat gggacacttc 300

atcctggccc gatgtccgaa aggagaaact ctgacggtgg gattcactga cggtaggaag 360

atcagtcact catgtacgca cccatttcac cacgaccctc ctgtgatagg ccgggaaaaa 420

tttcattccc gaccgcagca cggtagagaa ctaccttgca gcacgtacgc gcagagcacc 480

gctgcaactg ccgaggagat agaggtacat atgcccccag acaccccaga tcgcacattg 540

atgtcacaac agtccggtaa tgtaaagatc acagtcaata gtcagacggt gcggtacaag 600

tgtaattgcg gtgactcaaa tgaaggacta accactacag acaaagtgat taataactgc 660

aaggttgatc aatgccatgc cgcggtcacc aatcacaaaa aatggcagta taattcccct 720

ctggtcccgc gtaatgctga actcggggac cgaaaaggaa aagttcacat tccgtttcct 780

ctggcaaatg tgacatgcag ggtgcctaag gcaaggaacc ccaccgtgac gtacggaaaa 840

aaccaagtca tcatgctgct gtatcctgac cacccaacgc tcctgtccta ccggaatatg 900

ggagaagaac caaactatca agaagagtgg gtgacgcata agaaggagat caggttaacc 960

gtgccgactg aagggctcga ggtcacgtgg ggcaacaacg agccgtacaa gtattggccg 1020

cagttatcca caaacggtac agcccacggc cacccgcatg agataatttt gtattattat 1080

gagctgtacc ctactatgac tgtggtagtt gtgtcagtgg cctcgttcgt actcctgtcg 1140

atggtgggtg tggcagtggg gatgtgcatg tgtgcacgac gcagatgcat tacaccgtac 1200

gaactgacac caggagctac cgtccctttc ctgcttagcc taatatgctg cattagaaca 1260

gctaaagcg 1269

<210> 266
<211> 1269
<212> DNA
<213> Chikungunya virus

<400> 266
agtactaagg acaattttaa tgtctataaa gctacaagac catatctagc tcattgtcct 60

gactgcggag aagggcattc gtgccacagc cctatcgcat tggagcgcat cagaaatgaa 120

gcaacggacg gaacgctgaa aatccaggtc tctttgcaga tcgggataaa gacagatgac 180

agccacgatt ggaccaagct gcgctatatg gatagccata cgccagcgga cgcggagcga 240

gccggattgc ttgtaaggac ttcagcaccg tgcacgatca ccgggaccat gggacacttt 300

attctcgccc gatgcccgaa aggagagacg ctgacagtgg gatttacgga cagcagaaag 360

atcagccaca catgcacaca cccgttccat catgaaccac ctgtgatagg tagggagagg 420

ttccactctc gaccacaaca tggtaaagag ttaccttgca gcacgtacgt gcagagcacc 480

gctgccactg ccgaggagat agaggtgcat atgcccccag atactcctga ccgcacgctg 540

atgacgcagc agtctggcaa cgtgaagatc acagttaatg ggcagacggt gcggtacaag 600

tgcaactgcg gcggctcaaa cgagggactg acaaccacag acaaagtgat caataactgc 660

aaaattgatc agtgccatgc tgcagtcact aatcacaaga agtggcaata caactcccct 720

ttagtcccgc gtaacgctga actcggggac cgtaaaggaa agattcacat cccattccca 780

ttggcaaacg tgacttgcag agtgccaaaa gcaagaaacc ccacagtaac gtacggaaaa 840

aaccaagtca ccatgctgct gtatcctgac catccgacac tcttgtctta tcgtaacatg 900

ggacaggaac caaattacca cgaggagtgg gtgacacaca agaaggaggt taccttgacc 960

gtgcctactg agggtctgga ggtcacttgg ggcaacaacg aaccatacaa gtactggccg 1020

cagatgtcta cgaacggtac tgctcatggt cacccacatg agataatctt gtactattat 1080

gagctgtacc ccactatgac tgtaatcatt gtgtcggtgg cctcgttcgt gcttctgtcg 1140

atggtgggca cagcagtggg gatgtgtgtg tgcgcacggc gcagatgcat tacaccatat 1200

gaattaacac caggagccac cgttcccttt ctgctcagcc tgctatgttg cgtcagaacg 1260

accaaggcg 1269

<210> 267
<211> 1269
<212> DNA
<213> Chikungunya virus

<400> 267
agcaccaagg acaacttcaa tgtctataaa gccacaagac catacttagc tcactgtccc 60

gactgtggag aagggcactc gtgccatagt cccgtagcac tagaacgcat cagaaatgaa 120

gcgacagacg ggacgctgaa aatccaggtc tccttgcaaa tcggaataaa gacggatgac 180

agccacgatt ggaccaagct gcgttatatg gacaaccaca tgccagcaga cgcagagagg 240

gcggggctat ttgtaagaac atcagcaccg tgtacgatta ctggaacaat gggacacttc 300

atcctggccc gatgtccaaa aggggaaact ctgacggtgg gattcactga cagtaggaag 360

attagtcact catgtacgca cccatttcac cacgaccctc ctgtgatagg tcgggaaaaa 420

ttccattccc gaccgcagca cggtaaagag ctaccttgca gcacgtacgt gcagagcacc 480

gccgcaacta ccgaggagat agaggtacac atgcccccag acacccctga tcgcacatta 540

atgtcacaac agtccggcaa cgtaaagatc acagtcaatg gccagacggt gcggtacaag 600

tgtaattgcg gtggctcaaa tgaaggacta acaactacag acaaagtgat taataactgc 660

aaggttgatc aatgtcatgc cgcggtcacc aatcacaaaa agtggcagta taactcccct 720

ctggtcccgc gtaatgctga acttggggac cgaaaaggaa aaattcacat cccgtttccg 780

ctggcaaatg taacatgcag ggtgcctaaa gcaaggaacc ccaccgtgac gtacgggaaa 840

aaccaagtca tcatgctact gtatcctgac cacccaacac tcctgtccta ccggaatatg 900

ggagaagaac caaactatca agaagagtgg gtgatgcata agaaggaagt cgtgctaacc 960

gtgccgactg aagggctcga ggtcacgtgg ggcaacaacg agccgtataa gtattggccg 1020

cagttatcta caaacggtac agcccatggc cacccgcatg agataattct gtattattat 1080

gagctgtacc ccactatgac tgtagtagtt gtgtcagtgg ccacgttcat actcctgtcg 1140

atggtgggta tggcagcggg gatgtgcatg tgtgcacgac gcagatgcat cacaccgtat 1200

gaactgacac caggagctac cgtccctttc ctgcttagcc taatatgctg catcagaaca 1260

gctaaagcg 1269

<210> 268
<211> 1269
<212> DNA
<213> Chikungunya virus

<400> 268
agcaccaagg acaacttcaa tgtctataaa gccacaagac catacttagc tcactgtccc 60

gactgtggag aagggcactc gtgccatagt cccgtagcac tagaacgcat cagaaatgaa 120

gcgacagacg ggacgctgaa aatccaggtc tccttgcaaa tcggaataaa gacggacgac 180

agccacgatt ggaccaagct gcgttatatg gacaaccaca tgccagcaga cgcagagagg 240

gcggggctat ttgtaagaac atcagcaccg tgtacgatta ctggaacaat gggacacttc 300

atcctggccc gatgtccaaa aggggaaact ctgacggtgg gattcactga cagtaggaag 360

attagtcatt catgtacgca cccatttcac cacgaccctc ctgtgatagg tcgggaaaaa 420

ttccattccc gaccgcagca cggtaaagag ctaccttgca gcacgtacgt gcagagcacc 480

gccgcaacta ccgaggagat agaggtacac atgcccccag acacccctga tcgcacatta 540

atgtcacaac agtccggcaa cgtaaagatc acagtcaatg gccagacggt gcggtacaag 600

tgtaattgcg gtggctcaaa tgaaggacta acaactacag acaaagtgat taataactgc 660

aaggttgatc aatgtcatgc cgcggtcacc aatcacaaaa agtggcagta taactcccct 720

ctggtcccgc gtaatgctga acttggggac cgaaaaggaa aaattcacat cccgtttccg 780

ctggcaaatg taacatgcag ggtgcctaaa gcaaggaacc ccaccgtgac gtacgggaaa 840

aaccaagtca tcatgctact gtatcctgac cacccaacac tcctgtccta ccggaatatg 900

ggagaagaac caaactatca agaagagtgg gtgatgcata agaaggaagt cgtgctaacc 960

gtgccgactg aagggctcga ggtcacgtgg ggcaacaacg agccgtataa gtattggccg 1020

cagttatcta caaacggtac agcccatggc cacccgcatg agataattct gtattattat 1080

gagctgtacc ctactatgac tgtagtagtt gtgtcagtgg ccacgttcat actcctgtcg 1140

atggtgggta tggcagtggg gatgtgcatg tgtgcacgac gcagatgcat cacaccgtat 1200

gaactgacac caggagctac cgtccctttc ctgcttagcc taatatgctg catcagaaca 1260

gctaaagcg 1269

<210> 269
<211> 1269
<212> DNA
<213> Chikungunya virus

<400> 269
agcaccaagg acaacttcaa tgtctataaa gccacaagac catacctagc tcactgtccc 60

gactgtggag aagggcactc gtgccatagt cccgtagcac tagaacgcat cagaaatgaa 120

gcgacagacg ggacgctgaa aatccaggtc tccttgcaaa ttggaatagg gacggatgat 180

agccatgatt ggaccaagct gcgttacatg gacaatcaca taccagcaga cgcagggagg 240

gccgggctat ttgtaagaac atcagcacca tgcacgatta ctggaacaat gggacacttc 300

atcctggccc gatgtccgaa aggagaaact ctgacggtgg gattcactga cagtaggaag 360

attagtcact catgtacgca cccatttcac cacgaccctc ctgtgatagg ccgggaaaaa 420

ttccattccc gaccgcagca cggtaaagag ctaccttgca gcacgtacgt gcagagcaac 480

gccgcaactg ccgaggagat agaggtacac atgcccccag acacccctga tcgcacattg 540

ctgtcacaac agtccggcaa cgtaaagatc acagtcaata gtcagacggt gcggtataag 600

tgtaattgcg gtggctcaaa tgaaggacta ataactacag ataaagtgat taataactgc 660

aaggttgatc aatgtcatgc cgcggtcacc aatcacaaaa agtggcagta taactcccct 720

ctggtcccgc gtaacgctga actcggggac cgaaaaggaa aaattcacat cccgtttccg 780

ctggcaaatg taacatgcat ggtgcctaaa gcaaggaacc ccaccgtgac gtacgggaaa 840

aaccaagtca tcatgctact gtatcctgac cacccaacac tcctgtccta ccggagtatg 900

ggagaagaac caaactatca agaagagtgg gtgacgcaca agaaggaggt cgtgctaacc 960

gtgccgactg aagggctcga ggttacgtgg ggcaacaacg agccgtataa gtattggccg 1020

cagttatctg caaacggtac agcccacggc cacccgcatg agataatctt gtactattat 1080

gagctgtacc ctactatgac tgtagtagtt gtgtcagtgg cctcgttcat actcctgtcg 1140

atggtgggta tggcagtggg gatgtgcatg tgtgcacgac gcagatgcat cacaccatac 1200

gaactgacac caggagctac cgtccctttc ctgcttagcc taatatgctg catcagaaca 1260

gctaaagcg 1269

<210> 270
<211> 1269
<212> DNA
<213> Chikungunya virus

<400> 270
agtattaagg accacttcaa tgtctataaa gccacaagac cgtacctagc tcactgtccc 60

gactgtggag aagggcactc gtgccatagt cccgtagcgc tagaacgcat cagaaacgaa 120

gcgacagacg ggacgttgaa aatccaggtt tccttgcaaa tcggaataaa gacggatgat 180

agccatgatt ggaccaagct gcgttatatg gacaatcaca tgccagcaga cgcagagcgg 240

gccgggctat ttgtaagaac gtcagcaccg tgcacgatta ctggaacaat gggacacttc 300

attctggccc gatgtccgaa aggagaaact ctgacggcgg ggttcactga cggtaggaag 360

atcagtcact catgtacgca cccatttcac catgaccctc ctgtgatagg ccgggaaaaa 420

ttccattccc gaccgcagca cggtagggaa ctaccttgca gcacgtacgc gcagagcacc 480

gctgcaactg ccgaggagat agaggtacac atgcccccag acaccccaga tcgcacatta 540

atgtcacaac agtccggcaa tgtaaagatc acagtcaata gtcagacggt gcggtacaag 600

tgcaattgtg gtgactcaag tgaaggatta accactacag ataaagtgat taataactgc 660

aaggtcgatc aatgccatgc cgcggtcacc aatcacaaaa aatggcagta taattcccct 720

ctggtcccgc gtaatgctga attcggggac cggaaaggaa aagttcacat tccatttcct 780

ctggcaaatg tgacatgcag ggtgcctaaa gcaagaaacc ccaccgtgac gtacggaaaa 840

aaccaagtca tcatgttgct gtatcctgac cacccaacgc tcctgtccta caggaatatg 900

ggagaagaac caaactatca agaagagtgg gtgacgcata agaaggagat caggttaacc 960

gtgccgactg aggggctcga ggtcacgtgg ggtaacaatg agccgtacaa gtattggccg 1020

cagttatcca caaacggtac agcccacggc cacccgcatg agataattct gtattattat 1080

gagctgtacc caactatgac tgcggtagtt ttgtcagtgg cctcgttcat actcctgtcg 1140

atggtgggtg tggcagtggg gatgtgcatg tgtgcacgac gcagatgcat tacaccgtac 1200

gaactgacac caggagctac cgtccctttc ctgcttagcc taatatgctg cattagaaca 1260

gctaaagcg 1269

<210> 271
<211> 423
<212> PRT
<213> Chikungunya virus

<400> 271

Ser Thr Lys Asp Asn Phe Asn Val Tyr Lys Ala Thr Arg Pro Tyr Leu
1 5 10 15

Ala His Cys Pro Asp Cys Gly Glu Gly His Ser Cys His Ser Pro Ile
20 25 30

Ala Leu Glu Arg Ile Arg Asn Glu Ala Thr Asp Gly Thr Leu Lys Ile
35 40 45

Gln Val Ser Leu Gln Ile Gly Ile Lys Thr Asp Asp Ser His Asp Trp
50 55 60

Thr Lys Leu Arg Tyr Met Asp Ser His Thr Pro Ala Asp Ala Glu Arg
65 70 75 80

Ala Gly Leu Leu Val Arg Thr Ser Ala Pro Cys Thr Ile Thr Gly Thr
85 90 95

Met Gly His Phe Ile Leu Ala Arg Cys Pro Lys Gly Glu Thr Leu Thr
100 105 110

Val Gly Phe Thr Asp Ser Arg Lys Ile Ser His Thr Cys Thr His Pro
115 120 125

Phe His His Glu Pro Pro Val Ile Gly Arg Glu Arg Phe His Ser Arg
130 135 140

Pro Gln His Gly Lys Glu Leu Pro Cys Ser Thr Tyr Val Gln Ser Thr
145 150 155 160

Ala Ala Thr Ala Glu Glu Ile Glu Val His Met Pro Pro Asp Thr Pro
165 170 175

Asp Arg Thr Leu Met Thr Gln Gln Ser Gly Asn Val Lys Ile Thr Val
180 185 190

Asn Gly Gln Thr Val Arg Tyr Lys Cys Asn Cys Gly Gly Ser Asn Glu
195 200 205

Gly Leu Thr Thr Thr Asp Lys Val Ile Asn Asn Cys Lys Ile Asp Gln
210 215 220

Cys His Ala Ala Val Thr Asn His Lys Lys Trp Gln Tyr Asn Ser Pro
225 230 235 240

Leu Val Pro Arg Asn Ala Glu Leu Gly Asp Arg Lys Gly Lys Ile His
245 250 255

Ile Pro Phe Pro Leu Ala Asn Val Thr Cys Arg Val Pro Lys Ala Arg
260 265 270

Asn Pro Thr Val Thr Tyr Gly Lys Asn Gln Val Thr Met Leu Leu Tyr
275 280 285

Pro Asp His Pro Thr Leu Leu Ser Tyr Arg Asn Met Gly Gln Glu Pro
290 295 300

Asn Tyr His Glu Glu Trp Val Thr His Lys Lys Glu Val Thr Leu Thr
305 310 315 320

Val Pro Thr Glu Gly Leu Glu Val Thr Trp Gly Asn Asn Glu Pro Tyr
325 330 335

Lys Tyr Trp Pro Gln Met Ser Thr Asn Gly Thr Ala His Gly His Pro
340 345 350

His Glu Ile Ile Leu Tyr Tyr Tyr Glu Leu Tyr Pro Thr Met Thr Val
355 360 365

Ile Ile Val Ser Val Ala Ser Phe Val Leu Leu Ser Met Val Gly Thr
370 375 380

Ala Val Gly Met Cys Val Cys Ala Arg Arg Arg Cys Ile Thr Pro Tyr
385 390 395 400

Glu Leu Thr Pro Gly Ala Thr Val Pro Phe Leu Leu Ser Leu Leu Cys
405 410 415

Cys Val Arg Thr Thr Lys Ala
420

<210> 272
<211> 423
<212> PRT
<213> Chikungunya virus

<400> 272

Ser Ile Lys Asp His Phe Asn Val Tyr Lys Ala Thr Arg Pro Tyr Leu
1 5 10 15

Ala His Cys Pro Asp Cys Gly Glu Gly His Ser Cys His Ser Pro Val
20 25 30

Ala Leu Glu Arg Ile Arg Asn Glu Ala Thr Asp Gly Thr Leu Lys Ile
35 40 45

Gln Val Ser Leu Gln Ile Gly Ile Lys Thr Asp Asp Ser His Asp Trp
50 55 60

Thr Lys Leu Arg Tyr Met Asp Asn His Met Pro Ala Asp Ala Glu Arg
65 70 75 80

Ala Gly Leu Phe Val Arg Thr Ser Ala Pro Cys Thr Ile Thr Gly Thr
85 90 95

Met Gly His Phe Ile Leu Ala Arg Cys Pro Lys Gly Glu Thr Leu Thr
100 105 110

Ala Gly Phe Thr Asp Gly Arg Lys Ile Ser His Ser Cys Thr His Pro
115 120 125

Phe His His Asp Pro Pro Val Ile Gly Arg Glu Lys Phe His Ser Arg
130 135 140

Pro Gln His Gly Arg Glu Leu Pro Cys Ser Thr Tyr Ala Gln Ser Thr
145 150 155 160

Ala Ala Thr Ala Glu Glu Ile Glu Val His Met Pro Pro Asp Thr Pro
165 170 175

Asp Arg Thr Leu Met Ser Gln Gln Ser Gly Asn Val Lys Ile Thr Val
180 185 190

Asn Ser Gln Thr Val Arg Tyr Lys Cys Asn Cys Gly Asp Ser Ser Glu
195 200 205

Gly Leu Thr Thr Thr Asp Lys Val Ile Asn Asn Cys Lys Val Asp Gln
210 215 220

Cys His Ala Ala Val Thr Asn His Lys Lys Trp Gln Tyr Asn Ser Pro
225 230 235 240

Leu Val Pro Arg Asn Ala Glu Phe Gly Asp Arg Lys Gly Lys Val His
245 250 255

Ile Pro Phe Pro Leu Ala Asn Val Thr Cys Arg Val Pro Lys Ala Arg
260 265 270

Asn Pro Thr Val Thr Tyr Gly Lys Asn Gln Val Ile Met Leu Leu Tyr
275 280 285

Pro Asp His Pro Thr Leu Leu Ser Tyr Arg Asn Met Gly Glu Glu Pro
290 295 300

Asn Tyr Gln Glu Glu Trp Val Thr His Lys Lys Glu Ile Arg Leu Thr
305 310 315 320

Val Pro Thr Glu Gly Leu Glu Val Thr Trp Gly Asn Asn Glu Pro Tyr
325 330 335

Lys Tyr Trp Pro Gln Leu Ser Thr Asn Gly Thr Ala His Gly His Pro
340 345 350

His Glu Ile Ile Leu Tyr Tyr Tyr Glu Leu Tyr Pro Thr Met Thr Ala
355 360 365

Val Val Leu Ser Val Ala Ser Phe Ile Leu Leu Ser Met Val Gly Val
370 375 380

Ala Val Gly Met Cys Met Cys Ala Arg Arg Arg Cys Ile Thr Pro Tyr
385 390 395 400

Glu Leu Thr Pro Gly Ala Thr Val Pro Phe Leu Leu Ser Leu Ile Cys
405 410 415

Cys Ile Arg Thr Ala Lys Ala
420

<210> 273
<211> 423
<212> PRT
<213> Chikungunya virus

<400> 273

Ser Ile Lys Asp Asn Phe Asn Val Tyr Lys Ala Ile Arg Pro Tyr Leu

1 5 10 15

Ala His Cys Pro Asp Cys Gly Glu Gly His Ser Cys His Ser Pro Val
20 25 30

Ala Leu Glu Arg Ile Arg Asn Glu Ala Thr Asp Gly Thr Leu Lys Ile
35 40 45

Gln Val Ser Leu Gln Ile Gly Ile Lys Thr Asp Asp Ser His Asp Trp
50 55 60

Thr Lys Leu Arg Tyr Met Asp Asn His Met Pro Ala Asp Ala Glu Arg
65 70 75 80

Ala Arg Leu Phe Val Arg Thr Ser Ala Pro Cys Thr Ile Thr Gly Thr
85 90 95

Met Gly His Phe Ile Leu Ala Arg Cys Pro Lys Gly Glu Thr Leu Thr
100 105 110

Val Gly Phe Thr Asp Gly Arg Lys Ile Ser His Ser Cys Thr His Pro
115 120 125

Phe His His Asp Pro Pro Val Ile Gly Arg Glu Lys Phe His Ser Arg
130 135 140

Pro Gln His Gly Arg Glu Leu Pro Cys Ser Thr Tyr Ala Gln Ser Thr
145 150 155 160

Ala Ala Thr Ala Glu Glu Ile Glu Val His Met Pro Pro Asp Thr Pro
165 170 175

Asp Arg Thr Leu Met Ser Gln Gln Ser Gly Asn Val Lys Ile Thr Val
180 185 190

Asn Ser Gln Thr Val Arg Tyr Lys Cys Asn Cys Gly Asp Ser Asn Glu
195 200 205

Gly Leu Thr Thr Thr Asp Lys Val Ile Asn Asn Cys Lys Val Asp Gln
210 215 220

Cys His Ala Ala Val Thr Asn His Lys Lys Trp Gln Tyr Asn Ser Pro
225 230 235 240

Leu Val Pro Arg Asn Ala Glu Leu Gly Asp Arg Lys Gly Lys Val His
245 250 255

Ile Pro Phe Pro Leu Ala Asn Val Thr Cys Arg Val Pro Lys Ala Arg
260 265 270

Asn Pro Thr Val Thr Tyr Gly Lys Asn Gln Val Ile Met Leu Leu Tyr
275 280 285

Pro Asp His Pro Thr Leu Leu Ser Tyr Arg Asn Met Gly Glu Glu Pro
290 295 300

Asn Tyr Gln Glu Glu Trp Val Thr His Lys Lys Glu Ile Arg Leu Thr
305 310 315 320

Val Pro Thr Glu Gly Leu Glu Val Thr Trp Gly Asn Asn Glu Pro Tyr
325 330 335

Lys Tyr Trp Pro Gln Leu Ser Thr Asn Gly Thr Ala His Gly His Pro
340 345 350

His Glu Ile Ile Leu Tyr Tyr Tyr Glu Leu Tyr Pro Thr Met Thr Val
355 360 365

Val Val Val Ser Val Ala Ser Phe Val Leu Leu Ser Met Val Gly Val
370 375 380

Ala Val Gly Met Cys Met Cys Ala Arg Arg Arg Cys Ile Thr Pro Tyr
385 390 395 400

Glu Leu Thr Pro Gly Ala Thr Val Pro Phe Leu Leu Ser Leu Ile Cys
405 410 415

Cys Ile Arg Thr Ala Lys Ala
420

<210> 274
<211> 423
<212> PRT
<213> Chikungunya virus

<400> 274

Ser Thr Lys Asp Asn Phe Asn Val Tyr Lys Ala Thr Arg Pro Tyr Leu
1 5 10 15

Ala His Cys Pro Asp Cys Gly Glu Gly His Ser Cys His Ser Pro Val
20 25 30

Ala Leu Glu Arg Ile Arg Asn Glu Ala Thr Asp Gly Thr Leu Lys Ile
35 40 45

Gln Val Ser Leu Gln Ile Gly Ile Gly Thr Asp Asp Ser His Asp Trp
50 55 60

Thr Lys Leu Arg Tyr Met Asp Asn His Ile Pro Ala Asp Ala Gly Arg
65 70 75 80

Ala Gly Leu Phe Val Arg Thr Ser Ala Pro Cys Thr Ile Thr Gly Thr
85 90 95

Met Gly His Phe Ile Leu Ala Arg Cys Pro Lys Gly Glu Thr Leu Thr
100 105 110

Val Gly Phe Thr Asp Ser Arg Lys Ile Ser His Ser Cys Thr His Pro
115 120 125

Phe His His Asp Pro Pro Val Ile Gly Arg Glu Lys Phe His Ser Arg
130 135 140

Pro Gln His Gly Lys Glu Leu Pro Cys Ser Thr Tyr Val Gln Ser Asn
145 150 155 160

Ala Ala Thr Ala Glu Glu Ile Glu Val His Met Pro Pro Asp Thr Pro
165 170 175

Asp Arg Thr Leu Leu Ser Gln Gln Ser Gly Asn Val Lys Ile Thr Val
180 185 190

Asn Ser Gln Thr Val Arg Tyr Lys Cys Asn Cys Gly Gly Ser Asn Glu
195 200 205

Gly Leu Ile Thr Thr Asp Lys Val Ile Asn Asn Cys Lys Val Asp Gln
210 215 220

Cys His Ala Ala Val Thr Asn His Lys Lys Trp Gln Tyr Asn Ser Pro

225 230 235 240

Leu Val Pro Arg Asn Ala Glu Leu Gly Asp Arg Lys Gly Lys Ile His
245 250 255

Ile Pro Phe Pro Leu Ala Asn Val Thr Cys Met Val Pro Lys Ala Arg
260 265 270

Asn Pro Thr Val Thr Tyr Gly Lys Asn Gln Val Ile Met Leu Leu Tyr
275 280 285

Pro Asp His Pro Thr Leu Leu Ser Tyr Arg Ser Met Gly Glu Glu Pro
290 295 300

Asn Tyr Gln Glu Glu Trp Val Thr His Lys Lys Glu Val Val Leu Thr
305 310 315 320

Val Pro Thr Glu Gly Leu Glu Val Thr Trp Gly Asn Asn Glu Pro Tyr
325 330 335

Lys Tyr Trp Pro Gln Leu Ser Ala Asn Gly Thr Ala His Gly His Pro
340 345 350

His Glu Ile Ile Leu Tyr Tyr Tyr Glu Leu Tyr Pro Thr Met Thr Val
355 360 365

Val Val Val Ser Val Ala Ser Phe Ile Leu Leu Ser Met Val Gly Met
370 375 380

Ala Val Gly Met Cys Met Cys Ala Arg Arg Arg Cys Ile Thr Pro Tyr
385 390 395 400

Glu Leu Thr Pro Gly Ala Thr Val Pro Phe Leu Leu Ser Leu Ile Cys
405 410 415

Cys Ile Arg Thr Ala Lys Ala
420

<210> 275
<211> 423
<212> PRT
<213> Chikungunya virus

<400> 275

Ser Thr Lys Asp Asn Phe Asn Val Tyr Lys Ala Thr Arg Pro Tyr Leu
1 5 10 15

Ala His Cys Pro Asp Cys Gly Glu Gly His Ser Cys His Ser Pro Val
20 25 30

Ala Leu Glu Arg Ile Arg Asn Glu Ala Thr Asp Gly Thr Leu Lys Ile
35 40 45

Gln Val Ser Leu Gln Ile Gly Ile Lys Thr Asp Asp Ser His Asp Trp
50 55 60

Thr Lys Leu Arg Tyr Met Asp Asn His Met Pro Ala Asp Ala Glu Arg
65 70 75 80

Ala Gly Leu Phe Val Arg Thr Ser Ala Pro Cys Thr Ile Thr Gly Thr
85 90 95

Met Gly His Phe Ile Leu Ala Arg Cys Pro Lys Gly Glu Thr Leu Thr
100 105 110

Val Gly Phe Thr Asp Ser Arg Lys Ile Ser His Ser Cys Thr His Pro
115 120 125

Phe His His Asp Pro Pro Val Ile Gly Arg Glu Lys Phe His Ser Arg
130 135 140

Pro Gln His Gly Lys Glu Leu Pro Cys Ser Thr Tyr Val Gln Ser Thr
145 150 155 160

Ala Ala Thr Thr Glu Glu Ile Glu Val His Met Pro Pro Asp Thr Pro
165 170 175

Asp Arg Thr Leu Met Ser Gln Gln Ser Gly Asn Val Lys Ile Thr Val
180 185 190

Asn Gly Gln Thr Val Arg Tyr Lys Cys Asn Cys Gly Gly Ser Asn Glu
195 200 205

Gly Leu Thr Thr Thr Asp Lys Val Ile Asn Asn Cys Lys Val Asp Gln
210 215 220

Cys His Ala Ala Val Thr Asn His Lys Lys Trp Gln Tyr Asn Ser Pro
225 230 235 240

Leu Val Pro Arg Asn Ala Glu Leu Gly Asp Arg Lys Gly Lys Ile His
245 250 255

Ile Pro Phe Pro Leu Ala Asn Val Thr Cys Arg Val Pro Lys Ala Arg
260 265 270

Asn Pro Thr Val Thr Tyr Gly Lys Asn Gln Val Ile Met Leu Leu Tyr
275 280 285

Pro Asp His Pro Thr Leu Leu Ser Tyr Arg Asn Met Gly Glu Glu Pro
290 295 300

Asn Tyr Gln Glu Glu Trp Val Met His Lys Lys Glu Val Val Leu Thr
305 310 315 320

Val Pro Thr Glu Gly Leu Glu Val Thr Trp Gly Asn Asn Glu Pro Tyr
325 330 335

Lys Tyr Trp Pro Gln Leu Ser Thr Asn Gly Thr Ala His Gly His Pro
340 345 350

His Glu Ile Ile Leu Tyr Tyr Tyr Glu Leu Tyr Pro Thr Met Thr Val
355 360 365

Val Val Val Ser Val Ala Thr Phe Ile Leu Leu Ser Met Val Gly Met
370 375 380

Ala Val Gly Met Cys Met Cys Ala Arg Arg Arg Cys Ile Thr Pro Tyr
385 390 395 400

Glu Leu Thr Pro Gly Ala Thr Val Pro Phe Leu Leu Ser Leu Ile Cys
405 410 415

Cys Ile Arg Thr Ala Lys Ala
420

<210> 276
<211> 423
<212> PRT
<213> Chikungunya virus

<400> 276

Ser Thr Lys Asp Asn Phe Asn Val Tyr Lys Ala Thr Arg Pro Tyr Leu
1 5 10 15

Ala His Cys Pro Asp Cys Gly Glu Gly His Ser Cys His Ser Pro Val
20 25 30

Ala Leu Glu Arg Ile Arg Asn Glu Ala Thr Asp Gly Thr Leu Lys Ile
35 40 45

Gln Val Ser Leu Gln Ile Gly Ile Lys Thr Asp Asp Ser His Asp Trp
50 55 60

Thr Lys Leu Arg Tyr Met Asp Asn His Met Pro Ala Asp Ala Glu Arg
65 70 75 80

Ala Gly Leu Phe Val Arg Thr Ser Ala Pro Cys Thr Ile Thr Gly Thr
85 90 95

Met Gly His Phe Ile Leu Ala Arg Cys Pro Lys Gly Glu Thr Leu Thr
100 105 110

Val Gly Phe Thr Asp Ser Arg Lys Ile Ser His Ser Cys Thr His Pro
115 120 125

Phe His His Asp Pro Pro Val Ile Gly Arg Glu Lys Phe His Ser Arg
130 135 140

Pro Gln His Gly Lys Glu Leu Pro Cys Ser Thr Tyr Val Gln Ser Thr
145 150 155 160

Ala Ala Thr Thr Glu Glu Ile Glu Val His Met Pro Pro Asp Thr Pro
165 170 175

Asp Arg Thr Leu Met Ser Gln Gln Ser Gly Asn Val Lys Ile Thr Val
180 185 190

Asn Gly Gln Thr Val Arg Tyr Lys Cys Asn Cys Gly Gly Ser Asn Glu
195 200 205

Gly Leu Thr Thr Thr Asp Lys Val Ile Asn Asn Cys Lys Val Asp Gln
210 215 220

Cys His Ala Ala Val Thr Asn His Lys Lys Trp Gln Tyr Asn Ser Pro
225 230 235 240

Leu Val Pro Arg Asn Ala Glu Leu Gly Asp Arg Lys Gly Lys Ile His
245 250 255

Ile Pro Phe Pro Leu Ala Asn Val Thr Cys Arg Val Pro Lys Ala Arg
260 265 270

Asn Pro Thr Val Thr Tyr Gly Lys Asn Gln Val Ile Met Leu Leu Tyr
275 280 285

Pro Asp His Pro Thr Leu Leu Ser Tyr Arg Asn Met Gly Glu Glu Pro
290 295 300

Asn Tyr Gln Glu Glu Trp Val Met His Lys Lys Glu Val Val Leu Thr
305 310 315 320

Val Pro Thr Glu Gly Leu Glu Val Thr Trp Gly Asn Asn Glu Pro Tyr
325 330 335

Lys Tyr Trp Pro Gln Leu Ser Thr Asn Gly Thr Ala His Gly His Pro
340 345 350

His Glu Ile Ile Leu Tyr Tyr Tyr Glu Leu Tyr Pro Thr Met Thr Val
355 360 365

Val Val Val Ser Val Ala Thr Phe Ile Leu Leu Ser Met Val Gly Met
370 375 380

Ala Ala Gly Met Cys Met Cys Ala Arg Arg Arg Cys Ile Thr Pro Tyr
385 390 395 400

Glu Leu Thr Pro Gly Ala Thr Val Pro Phe Leu Leu Ser Leu Ile Cys
405 410 415

Cys Ile Arg Thr Ala Lys Ala
420

摘要

本发明涉及结合并中和切昆贡亚热病毒(Chikungunya virus)(CHIKV)的抗体及其使用方法。