TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]—Continued

Activity	No. of Recordkeepers	Annual Frequency per Record-keeping	Total Annual Records	Hours per Record	Total Hours
Total					135,095

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

C. Costs Associated With Electronic Submission

There are no capital costs or operating and maintenance costs associated with the transition from paper to electronic submissions. To create an SPL file and submit it to FDA, a registrant would need the following tools: A computer, appropriate software, access to the Internet, knowledge of terminology and standards, and access to FDA's ESG.

Registrants (and most individuals) have computers and Internet access available for their use. If a business does not have an available computer or access to the Internet, free use of computers and Internet are usually available at public facilities, e.g., a community library; or they may request a waiver from submitting the information electronically.

Software is necessary to create a ''document.'' The SPL file or ''document'' may be created internally by a business with experience with SPL or a business may use a user-friendly software (XForms)[3] available at no cost for industry use. In addition to the software, FDA also provides technical assistance, and other resources, terminology, and data standards regarding SPL files.[4]

Once the SPL file is created, the registrant would upload the file through the ESG. A digital certificate is needed to use the ESG. The digital certificate binds together the owner's name and a pair of electronic keys (a public key and a private key) that can be used to encrypt and sign documents. However, a small fee of up to $20.00 is charged for the digital certificate and the registrant may need to renew the certificate not less than annually. FDA is not calculating this small fee as cost of doing business because it is less than or equal to the biannual courier costs the registrant incurs for paper submissions.

[3] See *http://www.fda.gov/oc/datacouncil/xforms.html.*

[4] See *http://www.fda.gov/oc/datacouncil/spl.html.*

Dated: October 15, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E8–25338 Filed 10–22–08; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, HHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301–496–7057; fax: 301–402–0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Development of Mutations Useful for Attenuating Dengue Viruses and Chimeric Dengue Viruses

Description of Technology: Although flaviviruses cause a great deal of human suffering and economic loss, there is a shortage of effective vaccines. This invention relates to dengue virus mutations that may contribute to the development of improved dengue vaccines. Site directed and random mutagenesis techniques were used to introduce mutations into the dengue virus genome and to assemble a collection of useful mutations for incorporation in recombinant live attenuated dengue virus vaccines. The resulting mutant viruses were screened for several valuable phenotypes, including temperature sensitivity in Vero cells or human liver cells, host cell restriction in mosquito cells or human liver cells, host cell adaptation for improved replication in Vero cells, and attenuation in mice or in mosquitoes. The genetic basis for each observed phenotype was determined by direct sequence analysis of the genome of the mutant virus. Mutations identified through these sequencing efforts have been further evaluated by re-introduction of the identified mutations, singly, or in combination, into recombinant dengue virus and characterization of the resulting recombinant virus for phenotypes. In this manner, a menu of attenuating and growth promoting mutations was developed that is useful in fine-tuning the attenuation and growth characteristics of dengue virus vaccine candidates. The mutations promoting growth in Vero cells have usefulness for the production of live or inactivated dengue virus vaccines.

Inventors: Stephen S. Whitehead, Brian R. Murphy, Kathryn A. Hanley, Joseph E. Blaney (NIAID).

Patent Status: U.S. Patent No. 7,226,602 issued 05 Jun 2007 (HHS Reference No. E–120–2001/0–US–04); U.S. Patent Application No. 11/446,050 filed 02 Jun 2006 (HHS Reference No. E–120–2001/0–US–10).

Licensing Contact: Peter A. Soukas, J.D.; 301–435–4646; *soukasp@mail.nih.gov*.

Collaborative Research Opportunity: The National Institute of Allergy and Infectious Diseases, Laboratory of Infectious Diseases, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize these vaccines. Please contact Dr. Brian Murphy at 301–594–1616 or *bm25f@nih.gov* for more information.

Dengue Tetravalent Vaccine Containing a Common 30 Nucleotide Deletion in the 3′-UTR of Dengue Types 1, 2, 3, and 4

Description of Technology: The invention relates to a dengue virus

tetravalent vaccine containing a common 30-nucleotide deletion (Delta30) in the 3′-untranslated region (UTR) of the genome of dengue virus serotypes 1, 2, 3, and 4. The previously identified Delta30 attenuating mutation, created in dengue virus type 4 (DEN4) by the removal of 30 nucleotides from the 3′-UTR, is also capable of attenuating a wild-type strain of dengue virus type 1 (DEN1). Removal of 30 nucleotides from the DEN1 3′-UTR in a highly conserved region homologous to the DEN4 region encompassing the Delta30 mutation yielded a recombinant virus attenuated in rhesus monkeys to a level similar to recombinant virus DEN4Delta30. This established the transportability of the Delta30 mutation and its attenuation phenotype to a dengue virus type other than DEN4. The effective transferability of the Delta30 mutation establishes the usefulness of the Delta30 mutation to attenuate and improve the safety of commercializable dengue virus vaccines of any serotype.

A tetravalent dengue virus vaccine containing dengue virus types 1, 2, 3, and 4 each attenuated by the Delta30 mutation is being developed. The presence of the Delta30 attenuating mutation in each virus component precludes the reversion to a wild-type virus by intertypic recombination. In addition, because of the inherent genetic stability of deletion mutations, the Delta30 mutation represents an excellent alternative for use as a common mutation shared among each component of a tetravalent vaccine.

Inventors: Stephen S. Whitehead (NIAID), Brian R. Murphy (NIAID), Lewis Markoff (FDA), Barry Falgout (FDA), Kathryn A. Hanley (NIAID), Joseph E. Blaney (NIAID).

Patent Status: U.S. Patent Application No. 10/970,640 filed 21 Oct 2004, claiming priority to 03 May 2002 (HHS Reference No. E–089–2002/1–US–02)

Licensing Contact: Peter A. Soukas, J.D.; 301–435–4646; *soukasp@mail.nih.gov*.

Collaborative Research Opportunity: The National Institute of Allergy and Infectious Diseases, Laboratory of Infectious Diseases, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize these vaccines. Please contact Dr. Brian Murphy at 301–594–1616 or *bm25f@nih.gov* for more information.

Live Attenuated Vaccine to Prevent Disease Caused by West Nile Virus

Description of Technology: WNV has recently emerged in the U.S. and is considered a significant emerging disease that has embedded itself over a considerable region of the U.S. WNV infections have been recorded in humans as well as in different animals. To date, WNV has killed 294 people in the U.S. and caused severe disease in more than 4222 others. This project is part of NIAID's comprehensive emerging infectious disease program, which supports research on bacterial, viral, and other types of disease-causing microbes.

The methods and compositions of this invention provide a means for prevention of WNV infection by immunization with attenuated, immunogenic viral vaccines against WNV. The invention involves a chimeric virus form consisting of parts of WNV and Dengue virus. Construction of the hybrids and their properties are described in detail in AG Pletnev *et al.*, PNAS 2002; 99(5): 3036–3041.

The WNV chimeric vaccine does not target the central nervous system, which would be the case in an infection with wild type WNV. The vaccine stimulates strong anti-WNV immune responses, even following a single dose of the vaccine. When injected into mice, the vaccine protected all of the immunized animals from subsequent exposure to the New York WNV strain. The vaccine was also effective in primates.

The WNV vaccine may be used to protect the human population, particularly the elderly people, and domestic animals from WNV infection in the affected regions of the U.S. as well as worldwide.

Inventors: Alexander G. Pletnev *et al.* (NIAID).

Patent Status: U.S. Patent Application No. 10/871,775 filed 18 Jun 2004 (HHS Reference No. E–357–2001/1–US–02).

Licensing Status: Available for exclusive or non-exclusive licensing for developing a vaccine against WNV for humans or veterinary use in accordance with 35 U.S.C. 207 and 37 CFR Part 404.

Licensing Contact: Peter A. Soukas, J.D.; 301–435–4646; *soukasp@mail.nih.gov*.

Collaborative Research Opportunity: The National Institute of Allergy and Infectious Diseases is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, and commercialize this technology. Please contact Percy Pan at 301–451–3523 or *panp@niaid.nih.gov* for more information.

Development of Dengue Virus Type 3 Vaccine Candidates Containing Either (1) Nucleotide Deletions in the 3′-UTR of the Genome Consisting of More Than 30 Contiguous Nucleotides in One or Multiple Regions, or (2) a 3′-UTR Derived From DEN4 and Containing the A30 Nucleotide Deletion

Description of Technology: The disease burden associated with dengue virus infection has increased over the past several decades in the tropical and semi-tropical regions of the world, where over 2 billion people live at risk of dengue infection. Annually, there are an estimated fifty (50) to one hundred (100) million cases of dengue fever, making development of an effective vaccine a priority. In addition, there is a need for a ''travelers vaccine'' to protect those visiting dengue virus endemic areas, similar in scope to other currently available ''travelers vaccines'', such as hepatitis A vaccine.

The previously identified Δ30 attenuating mutation, created in each dengue virus serotype by the removal of 30 homologous nucleotides from the 3′-UTR, is capable of attenuating wild-type strains of dengue virus type 1 (DEN1), type 4 (DEN4) and to a limited extent type 2 (DEN2). These DEN1Delta30 and DEN4Delta30 viruses have been shown to be both safe and immunogenic in humans. However, the Delta30 mutation failed to have an attenuating effect on dengue virus type 3 (DEN3). To generate DEN3 vaccine candidates with a clearly attenuated phenotype, viruses were produced containing 3′-UTR deletions consisting of extensions of the original Delta30 mutation or additional mutations which remove stem-loop structures similar to those removed by Delta30. In addition, the entire 3′-UTR of DEN3 was replaced with the 3′-UTR derived from DEN4 and containing the Delta30 mutation. Studies in monkeys demonstrated that these newly developed viruses are highly attenuated, yet sufficiently immunogenic to warrant their further development for use as live attenuated vaccine candidates. Such viruses are anticipated to become the DEN3 component of a tetravalent vaccine formulation designed to immunize against all four dengue virus serotypes.

Application: Immunization against all four serotypes of Dengue Virus.

Developmental Status: Vaccine candidates have been synthesized and preclinical studies have been performed. The vaccine candidates of this invention are slated to enter Phase I clinical trials in the next year.

Inventors: Stephen S. Whitehead, Joseph E. Blaney, Brian R. Murphy (NIAID).

Patent Status: PCT Application No. PCT/US2007/076004 filed 15 Aug 2007, claiming priority to 15 Aug 2006 (HHS Reference No. E–139–2006/0–PCT–02).

Licensing Status: Available for exclusive or non-exclusive licensing.

Licensing Contact: Peter A. Soukas, J.D.; 301–435–4646; *soukasp@mail.nih.gov.*

Collaborative Research Opportunity: The National Institute of Allergy and Infectious Diseases, Laboratory of Infectious Diseases, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize these vaccines. Please contact Dr. Brian Murphy at 301–594–1616 or *bm25f@nih.gov* for more information.

Live Attenuated Virus Vaccines for La Crosse Virus and Other Bunyaviridae

Description of Technology: La Crosse virus (LACV), family *Bunyaviridae,* is a mosquito-borne pathogen endemic in the United States. LACV infection results in 70–130 clinical cases a year and is the major cause of pediatric arboviral encephalitis in North America. LACV was first identified as human pathogen in 1960 after its isolation from a 4 year-old girl from Minnesota who suffered meningoencephalitis and later died in La Crosse, Wisconsin. The majority of LACV infections are mild and never reported, however serologic studies estimate annual infection rates of 10–30/100,000 in endemic areas. LACV is a member of the California serogroup of viruses in the genus *Orthobunyavirus.* The serogroup contains members found on five continents that include human pathogens such as La Crosse, Snowshoe hare, and Jamestown Canyon viruses in North America; Guaroa virus in North and South America; Inkoo and Tahyna viruses in Europe; and Lumbo virus in Africa. Children who recover from severe La Crosse encephalitis may have significantly lower IQ scores than expected and a high prevalence (60% of those tested) of attention-deficit-hyperactivity disorder. Seizure disorders are also common in survivors. LACV can also cause encephalitis in immunosuppressed adults. Projected lifelong economic costs associated with neurologic sequelae range from $48,775–3,090,398 per case. At present, a vaccine or FDA approved antiviral therapy is not available.

This application principally claims live attenuated LACV vaccine compositions, but also includes subunit vaccine compositions including California encephalitis virus (CEV) serogroup immunogens, attenuated and inactivated CEV serogroup and chimeric *Bunyaviridae.* Also claimed are methods of treating or preventing CEV serogroup infection in a mammalian host, methods of producing a subunit vaccine composition, isolated polynucleotides comprising a nucleotide sequence encoding a CEV serogroup immunogen, methods for detecting LACV infection in a biological sample and infectious chimeric *Bunyaviridae.*

Application: Immunization against *Bunyaviridae.*

Developmental Status: Live attenuated vaccine candidates are currently being developed and preclinical studies in mice and monkeys are in progress. Suitable vaccine candidates will then be evaluated in clinical studies.

Inventors: Stephen S. Whitehead, Richard S. Bennett, Brian R. Murphy (NIAID)

Publication: RS Bennett et al. Genome sequence analysis of La Crosse virus and in vitro and in vivo phenotypes. Virol J. 2007 May 8;4:41.

Patent Status: PCT Application No. PCT/US2008/056099 filed 06 Mar 2008, claiming priority to 29 Mar 2007 (HHS Reference No. E–158–2007/3–PCT–01).

Licensing Status: Available for exclusive or non-exclusive licensing.

Licensing Contact: Peter A. Soukas, J.D.; 301–435–4646; *soukasp@mail.nih.gov.*

Collaborative Research Opportunity: The National Institute of Allergy and Infectious Diseases, Laboratory of Infectious Diseases, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize live attenuated virus vaccine candidates for La Crosse virus and other *Bunyaviridae.* Please contact Dr. Whitehead at 301–496–7692 for more information.

Development of Antigenic Chimeric St. Louis Encephalitis Virus/Dengue Virus Type Four Recombinant Viruses (SLEV/DEN4) as Vaccine Candidates for the Prevention of Disease Caused by SLEV

Description of Technology: St. Louis Encephalitis Virus (SLEV) is a mosquito-borne flavivirus that is endemic in the Americas and causes sporadic outbreaks of disease in humans. SLEV is a member of the Japanese encephalitis virus serocomplex and is closely related to West Nile Virus (WNV). St. Louis encephalitis is found throughout North, Central, and South America, and the Caribbean, but is a major public health problem mainly in the United States. Prior to the outbreak of West Nile virus in 1999, St. Louis encephalitis was the most common human disease caused by mosquitoes in the United States. Since 1964, there have been about 4,440 confirmed cases of St. Louis encephalitis, with an average of 130 cases per year. Up to 3,000 cases have been reported during epidemics in some years. Many more infections occur without symptoms and go undiagnosed. At present, a vaccine or FDA approved antiviral therapy is not available.

The inventors have previously developed a WNV/Dengue4Delta30 antigenic chimeric virus as a live attenuated virus vaccine candidate that contains the WNV premembrane and envelope (prM and E) proteins on a dengue virus type 4 (DEN4) genetic background with a thirty nucleotide deletion (Delta30) in the DEN4 3'-UTR. Using a similar strategy, the inventors have generated an antigenic chimeric virus, SLE/DEN4Delta30. Preclinical testing results indicate that chimerization of SLE with DEN4Delta30 decreased neuroinvasiveness in mice, did not affect neurovirulence in mice, and appeared to overattenuate the virus for non-human primates. Modifications of the SLE/DEN4Delta30 vaccine candidate are underway to improve its immunogenicity.

This application claims live attenuated chimeric SLE/DEN4Delta30 vaccine compositions and bivalent WNV/SLE/DEN4Delta30 vaccine compositions. Also claimed are methods of treating or preventing SLEV infection in a mammalian host, methods of producing a subunit vaccine composition, isolated polynucleotides comprising a nucleotide sequence encoding a SLEV immunogen, methods for detecting SLEV infection in a biological sample and infectious chimeric SLEV.

Application: Immunization against SLEV or SLEV and WNV.

Development Status: Live attenuated vaccine candidates are currently being developed and preclinical studies in mice and monkeys are in progress. Suitable vaccine candidates will then be evaluated in clinical studies.

Inventors: Stephen S. Whitehead, Joseph Blaney, Alexander Pletnev, Brian R. Murphy (NIAID).

Patent Status: PCT Application No. PCT/US2008/066445 filed 10 Jun 2008, claiming priority to 14 Jun 2007 (HHS Reference No. E–240–2007/0–PCT–02).

Licensing Status: Available for exclusive or non-exclusive licensing.

Licensing Contact: Peter A. Soukas, J.D.; 301–435–4646; *soukasp@mail.nih.gov.*

Collaborative Research Opportunity: The National Institute of Allergy and Infectious Diseases, Laboratory of Infectious Diseases, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize live attenuated virus vaccine candidates for St. Louis encephalitis virus. Please contact Dr. Whitehead at 301–496–7692 for more information.

Generation of Wild-Type Dengue Viruses for Use in Rhesus Monkey Infection Studies

Description of Technology: Dengue virus is a positive-sense RNA virus belonging to the *Flavivirus* genus of the family Flaviviridae. Dengue virus is widely distributed throughout the tropical and semitropical regions of the world and is transmitted to humans by mosquito vectors. Dengue virus is a leading cause of hospitalization and death in children in at least eight tropical Asian countries. There are four serotypes of dengue virus (DEN–1, DEN–2, DEN–3, and DEN–4) that annually cause an estimated 50–100 million cases of dengue fever and 500,000 cases of the more severe form of dengue virus infection known as dengue hemorrhagic fever/dengue shock syndrome (DHFIDSS). This latter disease is seen predominately in children and adults experiencing a second dengue virus infection with a serotype different than that of their first dengue virus infection and in primary infection of infants who still have circulating dengue-specific maternal antibody. A vaccine is needed to lessen the disease burden caused by dengue virus, but none is licensed.

Because of the association of more severe disease with secondary dengue virus infection, a successful vaccine must induce immunity to all four serotypes. Immunity is primarily mediated by neutralizing antibody directed against the envelope (E) glycoprotein, a virion structural protein. Infection with one serotype induces long-lived homotypic immunity and a short-lived heterotypic immunity. Therefore, the goal of immunization is to induce a long-lived neutralizing antibody response against DEN–1, DEN–2, DEN–3, and DEN–4, which can best be achieved economically using live attenuated virus vaccines. This is a reasonable goal since a live attenuated vaccine has already been developed for the related yellow fever virus, another mosquito-borne flavivirus present in tropical and semitropical regions of the world.

The evaluation of live attenuated dengue vaccine candidates in rhesus monkeys requires wild type control viruses for each of the four dengue serotypes. These control viruses are used for comparison to the attenuated strains and post-vaccination challenge to assess vaccine efficacy. As such, these viruses need to be well characterized and sufficiently pure to ensure that they will replicate to consistent levels in rhesus monkeys. Characterization generally includes sequence analysis, titration, and evaluation in monkeys. The following viruses have been characterized: (1) DEN1 WP (2) DEN1 Puerto Rico/94 (3) DEN2 NGC prototype (4) DEN2 Tonga/74 (5) DEN3 Sleman/78 and (6) DEN4 Dominica/81.

Application: Dengue/flavivirus vaccine studies, dengue/flavivirus diagnostics, dengue/flavivirus research tools.

Development Status: Materials are available for transfer.

Inventors: Stephen S. Whitehead and Joseph E. Blaney, Jr. (NIAID).

Publications:

1. AP Durbin, RA Karron, W Sun, DW Vaughn, MJ Reynolds, JR Perreault, B Thumar, R Men, C-J Lai, WR Elkins, RM Chanock, BR Murphy, SS Whitehead. A live attenuated dengue virus type 4 vaccine candidate with a 30 nucleotide deletion in the 3′ untranslated region is highly attenuated and immunogenic in humans. Am J Trop Med Hyg. 2001 Nov; 65(5): 405–413.

2. SS Whitehead, B Falgout, KA Hanley, JE Blaney Jr., L Markoff, BR Murphy. A live, attenuated dengue virus type 1 vaccine candidate with a 30-nucleotide deletion in the 3′ untranslated region is highly attenuated and immunogenic in monkeys. J Virol. 2003 Jan; 77(2): 1653–1657.

3. SS Whitehead, KA Hanley, JE Blaney Jr., LE Gilmore, WR Elkins, BR Murphy. Substitution of the structural genes of dengue virus type 4 with those of type 2 results in chimeric vaccine candidates which are attenuated for mosquitoes, mice, and rhesus monkeys. Vaccine 2003 Oct 1; 21(27–30): 4307–4316.

4. JE Blaney Jr., CT Hanson, KA Hanley, BR Murphy, SS Whitehead. Vaccine candidates derived from a novel infectious cDNA clone of an American genotype dengue virus type 2. BMC Infect Dis. 2004 Oct 4;4:39.

5. JE Blaney Jr., CT Hanson, CY Firestone, KA Hanley, BR Murphy, SS Whitehead. Genetically modified, live attenuated dengue virus type 3 vaccine candidates. Am J Trop Med Hyg. 2004 Dec; 71(6): 811–821.

6. JE Blaney Jr., JM Matro, BR Murphy, SS Whitehead. Recombinant, live-attenuated tetravalent dengue virus vaccine formulations induce a balanced, broad, and protective neutralizing antibody response against each of the four serotypes in rhesus monkeys. J Virol. 2005 May; 79(9): 5516–5528.

7. JE Blaney Jr., NS Sathe, CT Hanson, CY Firestone, BR Murphy, SS Whitehead. Vaccine candidates for dengue virus type 1 (DEN1) generated by replacement of the structural genes of rDEN4 and rDEN4Delta30 with those of DEN1. Virol J. 2007 Feb 28; 4:23.

Patent Status: HHS Reference No. E–042–2008/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Status: Available for nonexclusive biological materials licensing only.

Licensing Contact: Peter A. Soukas, J.D.; 301–435–4646; *soukasp@mail.nih.gov.*

Monoclonal Antibodies Against Dengue and Other Viruses With Deletion in Fc Region

Description of Technology: The four dengue virus (DENV) serotypes (DENV–1 to DENV–4) are the most important arthropod-borne flaviviruses in terms of morbidity and geographic distribution. Up to 100 million DENV infections occur every year, mostly in tropical and subtropical areas where vector mosquitoes are abundant. Infection with any of the DENV serotypes may be asymptomatic or may lead to classic dengue fever or more severe dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which are increasingly common in the dengue endemic areas. Immunity to the same virus serotype (homotypic immunity) is life-long, whereas immunity to different serotypes (heterotypic immunity) lasts 2–3 months so that infection with a different serotype virus is possible. DHF/DSS often occurs in patients with second, heterotypic DENV infections or in infants with maternally transferred dengue immunity. Severe dengue is a major cause of hospitalization, and fatality rates vary from <1% to 5% in children.

Antibody-dependent enhancement (ADE) has been proposed as an underlying pathogenic mechanism of DHF/DSS. ADE occurs because preexisting subneutralizing antibodies and the infecting DENV form complexes that bind to Fc receptor-bearing cells, leading to increased virus uptake and replication. ADE has been repeatedly demonstrated in vitro using dengue immune sera or monoclonal antibodies and cells of monocytic and recently, B

lymphocytic lineages bearing Fc receptors. ADE of DENV–2 infection has also been demonstrated in monkeys infused with a human dengue immune serum.

We have identified chimpanzee-human chimeric IgG1 mAbs capable of neutralizing or binding to one or more DENV serotypes. Cross-reactive IgG 1A5 neutralizes DENV–1 and DENV–2 more efficiently than DENV–3 and DENV–4, and type-specific IgG 5H2 neutralizes DENV–4 at a high titer. Analysis of antigenic variants has localized the IgG 1A5 binding site to the conserved fusion peptide in E. Thus, IgG 1A5 shares many characteristics with the cross-reactive antibodies detected in flavivirus infections.

This application claims a variant of an antibody comprising a polypeptide in the Fc region, which binds an Fc gamma receptor (FcgammaR) with lower affinity than the parent antibody. The variant polypeptide comprises a deletion of nine amino acids at the N-terminus of the C_H2 domain in the Fc region. Introduction of the Fc variant abrogates the antibody-mediated dengue virus replication enhancing activity. This invention has important implications for the antibody-mediated prevention of dengue virus infection.

Application: Immunization against Dengue and/or flaviviruses.

Developmental Status: Antibody candidates have been synthesized and preclinical studies have been performed.

Inventors: Ana Goncalvez, Robert Purcell, C.J. Lai (NIAID).

Publication: AP Goncalvez *et. al.* Monoclonal antibody-mediated enhancement of dengue virus infection in vitro and in vivo and strategies for prevention. Proc Natl Acad Sci USA. 2007 May 29; 104(22): 9422–9427.

Patent Status: PCT Application No. PCT/US2008/059313 filed 03 Apr 2008, claiming priority to 04 Apr 2007 (HHS Reference No. E–159–2007/3–PCT–01).

Licensing Status: Available for exclusive or non-exclusive licensing.

Licensing Contact: Peter A. Soukas, J.D.; 301–435–4646; *soukasp@mail.nih.gov.*

Monoclonal Antibodies That Bind or Neutralize Dengue Virus

Description of Technology: Among the arthropod-borne flaviviruses, the four dengue virus serotypes, dengue type 1 virus (DENV–1), dengue type 2 virus (DENV–2), dengue type 3 virus (DENV–3), and dengue type 4 virus (DENV–4 are most important in terms of human morbidity and geographic distribution. Dengue viruses cause dengue outbreaks and major epidemics in most tropical and subtropical areas where *Aedes albopictus* and *Aedes aegypti* mosquitoes are abundant. Dengue infection produces fever, rash, and joint pain in humans. A more severe and life-threatening form of dengue, characterized by hemorrhagic fever and hemorrhagic shock, has occurred with increasing frequency in Southeast Asia and Central and South America, where all four dengue virus serotypes circulate. A safe and effective vaccine against dengue is currently not available. Passive immunization with monoclonal antibodies from non-human primates or humans represents a possible alternative to vaccines for prevention of illness caused by dengue virus.

The application claims monoclonal antibodies that bind or neutralize dengue type 1, 2, 3, and/or 4 viruses. The application also claims fragments of such antibodies retaining dengue virus-binding ability, fully human or humanized antibodies retaining dengue virus-binding ability, and pharmaceutical compositions including such antibodies. The application also claims isolated nucleic acids encoding the antibodies of the invention. Additionally, application claims prophylactic, therapeutic, and diagnostic methods employing the antibodies and nucleic acids of the invention.

Application: Prophylaxis against dengue serotypes 1, 2, 3 and 4.

Development Status: Antibodies have been synthesized and preclinical studies have been performed.

Inventors: Ching-Juh Lai and Robert Purcell (NIAID).

Publications: The antibodies are further described in:

1. R Men *et al.* Identification of chimpanzee Fab fragments by repertoire cloning and production of a full-length humanized immunoglobulin G1 antibody that is highly efficient for neutralization of dengue type 4 virus. J Virol. 2004 May; 78(9): 4665–4674.

2. AP Goncalvez *et al.* Chimpanzee Fab fragments and a derived humanized immunoglobulin G1 antibody that efficiently cross-neutralize dengue type 1 and type 2 viruses. J Virol. 2004 Dec; 78(23): 12910–12918.

3. AP Goncalvez *et al.* Epitope determinants of a chimpanzee Fab antibody that efficiently cross-neutralizes dengue type 1 and type 2 viruses map to inside and in close proximity to fusion loop of the dengue type 2 virus envelope glycoprotein. J Virol. 2004 Dec; 78(23): 12919–12928.

4. AP Goncalvez *et al.* Monoclonal antibody-mediated enhancement of dengue virus infection in vitro and in vivo and strategies for prevention. Proc Natl Acad Sci U.S.A. 2007 May 29; 104(22): 9422–9427.

Patent Status: U.S. Patent Application No. 10/582,006 filed 07 Jun 2006 (HHS Reference No. E–066–2003/5–US–02); Canadian Patent Application No. 2548808 filed 03 Dec 2004 (HHS Reference No. E–066–2003/5–CA–03).

Licensing Status: Available for exclusive or non-exclusive licensing.

Licensing Contact: Peter A. Soukas, J.D.; 301–435–4646; *soukasp@mail.nih.gov.*

Collaborative Research Opportunity: The National Institute of Allergy and Infectious Diseases, Laboratory of Infectious Diseases, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize this technology. Please contact Ching-Juh Lai at 301–594–2422 for more information.

Dated: October 14, 2008.

Richard U. Rodriguez,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. E8–25210 Filed 10–22–08; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, HHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301–496–7057; fax: 301–402–0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.