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 (Δ30) in the 3′-untranslated region (UTR) of the genome of dengue virus serotypes 1, 2, 3, and 4. The previously identified Δ30 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 Δ30 mutation yielded a recombinant virus attenuated in rhesus monkeys to a level similar to recombinant virus DEN4Δ30. This established the transportability of the Δ30 mutation and its attenuation phenotype to a dengue virus type other than DEN4. The effective transferability of the Δ30 mutation establishes the usefulness of the Δ30 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 Δ30 mutation is being developed. The presence of the Δ30 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 Δ30 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.

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.

Date: January 10, 2008.

Steven M. Ferguson,

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

[FR Doc. E8–1234 Filed 1–24–08; 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.

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

Description of Invention: 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: U.S. Provisional Application No. 60/922,282 filed 04 Apr 2007 (HHS Reference No. E–159–2007/0–US–01); U.S. Provisional Application No. 60/927,755 filed 04 May 2007 (HHS Reference No. E–159–2007/1–US–01); U.S. Provisional Application No. 60/928,405 filed 08 May 2007 (HHS Reference No. E–159–2007/2–US–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 Neutralize *B. anthracis* Protective Antigen (PA), Lethal Factor (LF) and Edema Factor (EF)

Description of Invention: Anthrax, whether resulting from natural or bioterrorist-associated exposure, is a constant threat to human health. The lethality of anthrax is primarily the result of the effects of anthrax toxin, which has 3 components: a receptor-binding protein known as ''protective antigen'' (PA) and 2 catalytic proteins known as ''lethal factor'' (LF) and ''edema factor'' (EF). Although production of an efficient anthrax vaccine is an ultimate goal, the benefits of vaccination can be expected only if a large proportion of the population at risk is immunized. The low incidence of anthrax suggests that large-scale vaccination may not be the most efficient means of controlling this disease. In contrast, passive administration of neutralizing human or chimpanzee monoclonal antibody to a subject at risk for anthrax or exposed to anthrax could provide immediate efficacy for emergency prophylaxis against or treatment of anthrax.

Four monoclonal antibodies (mAbs) against PA, three mAbs against LF and four mAbs specific for EF of anthrax were isolated from a phage display library generated from immunized chimpanzees. Two mAbs recognizing PA (W1 and W2), two anti-LF mAbs efficiently neutralized the cytotoxicity of lethal toxin in a macrophage lysis assay. One anti-EF mAb efficiently neutralized edema toxin in cell culture. All five neutralizing mAbs protected animals from anthrax toxin challenge.

Application: Prophylactics or therapeutics against *B. anthracis.*

Developmental Status: Preclinical studies have been performed.

Inventors: Zhaochun Chen, Robert Purcell, Suzanne Emerson, Stephen Leppla, Mahtab Moyeri (NIAID).

Publication: Z Chen, *et al.* Efficient neutralization of anthrax toxin by chimpanzee monoclonal antibodies against protective antigen. J Infect Dis. 2006 Mar 1;193(5):625–633.

Patent Status: U.S. Provisional Application No. 60/903,022 filed 23 Feb 2007 (HHS Reference No. E–123–2007/0–US–01); U.S. Patent Application No. 11/793,735 filed 22 Jun 2007 (HHS Reference No. E–146–2004/0–US–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 Chimpanzee/human neutralizing monoclonal antibodies against anthrax toxins. Please contact Dr. Robert Purcell at 301–496–5090 for more information.

Cell-Nanofiber Composite and Cell-Nanofiber Composite Amalgam Based Engineered Intervertebral Disc

Description of Invention: Diseased or damaged musculoskeletal tissues are often replaced by an artificial material, cadaver tissue or donated, allogenic tissue. Tissue engineering offers an attractive alternative whereby a live, natural tissue is generated from a construct made up of a patient's own cells or an acceptable/compatible cell source in combination with a biodegradable scaffold for replacement of defective tissue.

Degeneration of the intervertebral disc (IVD) is a common and significant source of morbidity in our society. Approximately 8 of 10 adults at some point in their life will experience an episode of significant low back pain, with the majority improving without any formal treatment. However, for the subject requiring surgical management current interventions focus on fusion of the involved IVD levels, which eliminates pain but does not attempt to restore disc function. Approximately 200,000 spinal fusions were performed in the United States in 2002 to treat pain associated with lumbar disc degeneration. Spinal fusion however is thought to significantly alter the

biomechanics of the disc and lead to further degeneration, or adjacent segment disease. Therefore, in the past decade there has been mounting interest in the concept of IVD replacement. The replacement of the IVD holds tremendous potential as an alternative to spinal fusion for the treatment of degenerative disc disease by offering a safer alternative to current spinal fusion practices.

At the present time, several disc replacement implants are at different stages of preclinical and clinical testing. These disc replacement technologies are designed to address flexion, extension, and lateral bending motions; however, they do little to address compressive forces and their longevity is limited due to their inability to biointegrate. Therefore, a cell-based tissue engineering approach offers the most promising alternative to replace the degenerated IVD. Current treatment for injuries that penetrate subchondral bone include subchondral drilling, periosteal tissue grafting, osteochondral allografting, chondrogenic cell and transplantation; but are limited due to suboptimal integration with host tissues.

The present invention claims tissue engineered intervertebral discs comprising a nanofibrous polymer hydrogel amalgam having cells dispersed therein, methods of fabricating tissue engineered intervertebral discs by culturing a mixture of stem cells or intervertebral disc cells and a electrospun nanofibrous polymer hydrogel amalgam in a suitable bioreactor, and methods of treatment comprising implantation of tissue engineered intervertebral disc into a subject.

Application: Intervertebral disc bio-constructs and electrospinning methods for fabrication of the discs.

Developmental Status: Prototype devices have been fabricated and preclinical studies have been performed.

Inventors: Wan-Ju Li, Leon Nesti, Rocky Tuan (NIAMS)

Patent Status: U.S. Provisional Application No. 60/847,839 filed 27 Sep 2006 (HHS Reference No. E–309–2006/0–US–01); U.S. Provisional Application No. 60/848,284 filed 28 Sep 2006 (HHS Reference No. E–309–2006/1–US–01)

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

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

Cell-Nanofiber Composite Based Engineered Cartilage

Description of Invention: Available for licensing and commercial development is a tissue-engineered cartilage derived from a cellular composite made from a biodegradable, biocompatible polymeric nanofibrous matrix having dispersed chondrocytes or adult mesenchymal stem cells. More particularly, tissue-engineered cartilage can be prepared where the cartilage has a biodegradable and biocompatible nanofibrous polymer matrix prepared by electrospinning and a plurality of chondrocytes or mesenchymal stem cells dispersed in the pores of the matrix. The tissue-engineered cartilage possesses compressive strength properties similar to natural cartilage.

The electrospinning process is a simple, economical means to produce biomaterial matrices or scaffolds of ultra-fine fibers derived from a variety of biodegradable polymers (Li WJ, *et al. J. Biomed. Mater. Res.* 2002; 60:613–21). Nanofibrous scaffolds (NFSs) formed by electrospinning, by virtue of structural similarity to natural extracellular matrix (ECM), may represent promising structures for tissue engineering applications. Electrospun three-dimensional NFSs are characterized by high porosity with a wide distribution of pore diameter, high-surface area to volume ratio and morphological similarities to natural collagen fibrils (Li WJ, *et al. J. Biomed. Mater. Res.* 2002; 60:613–21). These physical characteristics promote favorable biological responses of seeded cells in vitro and in vivo, including enhanced cell attachment, proliferation, maintenance of the chondrocytic phenotype (Li WJ, *et al. J. Biomed. Mater. Res.* 2003; 67A: 1105–14), and support of chondrogenic differentiation (Li WJ, *et al. Biomaterials* 2005; 26:599–609) as well as other connective tissue linage differentiation (Li WJ, *et al. Biomaterials* 2005; 26:5158–5166). The invention based on cell-nanofiber composite represents a candidate engineered tissue for cell-based approaches to cartilage repair.

Application: Cartilage repair and methods for making tissue-engineered cartilage.

Developmental Status: Electrospinning method is fully developed and cartilage has been synthesized.

Inventors: Wan-Ju Li and Rocky Tuan (NIAMS).

Publications: The invention is further described in:

1. W-J Li, *et al.* Engineering controllable anisotropy in electrospun biodegradable nanofibrous scaffolds for musculoskeletal tissue engineering. J Biomech. 2007;40(8):1686–1693.

2. W-J Li, *et al.* Fabrication and characterization of six electrospun poly(alpha-hydroxy ester)-based fibrous scaffolds for tissue engineering applications. Acta Biomater. 2006 Jul;2(4):377–385.

3. CK Kuo, *et al.* Cartilage tissue engineering: its potential and uses. Curr Opin Rheumatol. 2006 Jan;18(1):64–73. Review.

4. W-J Li, *et al.* Multilineage differentiation of human mesenchymal stem cells in a three-dimensional nanofibrous scaffold. Biomaterials. 2005 Sep;26(25):5158–5166.

Patent Status: U.S. Provisional Application No. 60/690,998 filed 15 Jun 2005 (HHS Reference No. E–116–2005/0–US–01); PCT Application No. PCT/US2006/0237477 filed 15 Jun 2006 (HHS Reference No. E–116–2005/0–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.*

Methods for Preparing Complex Multivalent Immunogenic Conjugates

Description of Invention: Claimed in this application are novel methods for preparing complex multivalent immunogenic conjugates and conjugate vaccines. The multivalent conjugates and conjugate vaccines are synthesized by conjugating mixtures of more than one polysaccharide at a desired ratio of the component polysaccharides to at least one carrier protein using hydrazide chemistry. Because of the high efficiency of hydrazide chemistry in conjugation, the polysaccharides are effectively conjugated to the carrier protein(s) so that the resulting complex synthesized vaccine conjugate products, without requiring tedious and complicated purification procedures such as chromatography and/or ammonium sulfate precipitation, are efficacious in inducing antibodies in mice against each component polysaccharide. The methods claimed in this application simplify the preparation of multivalent conjugate vaccines by utilizing simultaneous conjugation reactions in a single reaction mixture or batch that includes at least two immunogenic-distinct polysaccharides. This single-batch simultaneous reaction eliminates the need for multiple parallel synthesis processes for each polysaccharide vaccine conjugate component as employed in conventional methods for making multivalent conjugate vaccines.

Application: Cost effective and efficient manufacturing of conjugate vaccines.

Inventors: Che-Hung Robert Lee (CBER/FDA)

Patent Status: PCT Application No. PCT/US2007/006627 filed 16 Mar 2007 (HHS Reference No. E–085–2005/0–PCT–02).

Licensing Status: Available for exclusive or non-exclusive licensing. The technology is not available for licensing in the field of use of multivalent meningitis vaccines.

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

Bioreactor Device and Method and System for Fabricating Tissue

Description of Invention: Available for licensing and commercial development is a millifluidic bioreactor system for culturing, testing, and fabricating natural or engineered cells and tissues. The system consists of a millifluidic bioreactor device and methods for sample culture. Biologic samples that can be utilized include cells, scaffolds, tissue explants, and organoids. The system is microchip controlled and can be operated in closed-loop, providing controlled delivery of medium and biofactors in a sterile temperature regulated environment under tabletop or incubator use. Sample perfusion can be applied periodically or continuously, in a bidirectional or unidirectional manner, and medium re-circulated.

Advantages: The device is small in size, and of conventional culture plate format.

Provides the ability to grow larger biologic samples than microfluidic systems, while utilizing smaller medium volumes than conventional bioreactors. The bioreactor culture chamber is adapted to contain sample volumes on a milliliter scale (10 [mu]L to 1 mL, with a preferred size of 100 [mu]L), significantly larger than chamber volumes in microfluidic systems (on the order of 1 [mu]L). Typical microfluidic systems are designed to culture cells and not larger tissue samples.

The integrated medium reservoirs and bioreactor chamber design provide for, (1) concentration of biofactors produced by the biologic sample, and (2) the use of smaller amounts of exogenous biofactor supplements in the culture medium. The local medium volume (within the vicinity of the sample) is less than twice the sample volume. The total medium volume utilized is small, preferably 2 ml, significantly smaller than conventional bioreactors (typically using 500–1,000 mL).

Provides for real-time monitoring of sample growth and function in response to stimuli via an optical port and embedded sensors. The optical port provides for microscopy and spectroscopy measurements using transmitted, reflected, or emitted (e.g., fluorescent, chemiluminescent) light. The embedded sensors provide for measurement of culture fluid pressure and sample pH, oxygen tension, and temperature.

Capable of providing external stimulation to the biologic sample, including mechanical forces (e.g. fluid shear, hydrostatic pressure, matrix compression, microgravity via clinorotation), electrical fields (e.g., AC currents), and biofactors (e.g., growth factors, cytokines) while monitoring their effect in real-time via the embedded sensors, optical port, and medium sampling port.

Monitoring of biologic sample response to external stimulation can be performed non-invasively and non-destructively through the embedded sensors, optical port, and medium sampling port. Testing of tissue mechanical and electrical properties (e.g., stiffness, permeability, loss modulus via stress or creep test, electrical impedance) can be performed over time without removing the sample from the bioreactor device.

The bioreactor sample chamber can be constructed with multiple levels fed via separate perfusion circuits, facilitating the growth and production of multiphasic tissues.

Application: Cartilage repair and methods for making tissue-engineered cartilage.

Development Stage: Electrospinning method is fully developed and cartilage has been synthesized.

Inventors: Juan M. Taboas (NIAMS), Rocky S. Tuan (NIAMS), *et al.*

Patent Status: U.S. Provisional Application No. 60/701,186 filed 20 Jul 2005 (HHS Reference No. E–042–2005/0–US–01); PCT Application No. PCT/US2006/028417 filed 20 Jul 2006, which published as WO 2007/012071 on 25 Jan 2007 (HHS Reference No. E–042–2005/0–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*.

Monoclonal Antibodies Against Orthopoxviruses

Description of Invention: Concerns that variola (smallpox) virus might be used as a biological weapon have led to the recommendation of widespread vaccination with vaccinia virus. While vaccination is generally safe and effective for prevention of smallpox, it is well documented that various adverse reactions in individuals have been caused by vaccination with existing licensed vaccines. Vaccinia immune globulin (VIG) prepared from vaccinated humans has historically been used to treat adverse reactions arising from vaccinia immunization. However, VIG lots may have different potencies and carry the potential to transmit other viral agents.

Chimpanzee Fabs against the B5 and A33 outer extracellular membrane proteins of vaccinia virus were isolated and converted into complete mAbs with human gamma1 heavy chain constant regions. The two mAbs displayed high binding affinities to B5 and A33. The mAbs inhibited the spread of vaccinia virus as well as variola virus (the causative agent of smallpox) *in vitro*, protected mice from subsequent intranasal challenge with virulent vaccinia virus, protected mice when administered 2 days after challenge, and provided significantly greater protection than that afforded by VIG.

Application: Prophylactics or therapeutics against orthopoxviruses.

Developmental Status: Preclinical studies have been performed.

Inventors: Zhaochun Chen, Robert Purcell, Suzanne Emerson, Patricia Earl, Bernard Moss (NIAID).

Publications:

1. Z Chen, *et al.* Chimpanzee/human mAbs to vaccinia virus B5 protein neutralize vaccinia and smallpox viruses and protect mice against vaccinia virus. Proc Natl Acad Sci USA. 2006 Feb 7;103(6):1882–1887. Epub 2006 Jan 25.

2. Z Chen, *et al.* Characterization of chimpanzee/human monoclonal antibodies to the vaccinia A33 glycoprotein and its variola virus homolog in vitro and in a vaccinia mouse protection model. J Virol. 2007 Jun 20; Epub ahead of print, doi 10.1128/JVI.00906–07.

Patent Status: PCT Patent Application No. PCT/US2006/048832 filed 22 Dec 2006 (HHS Reference No. E–145–2004/3–PCT–01); PCT Patent Application No. PCT/US2006/048833 filed 22 Dec 2006 (HHS Reference No. E–145–2004/4–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 Chimpanzee/human neutralizing monoclonal antibodies against orthopoxviruses. Please contact Dr. Robert Purcell at 301–496 5090 for more information.

A Method With Increased Yield for Production of Polysaccharide-Protein Conjugate Vaccines Using Hydrazide Chemistry

Description of Invention: Current methods for synthesis and manufacturing of polysaccharide-protein conjugate vaccines employ conjugation reactions with low efficiency (about twenty percent). This means that up to eighty percent of the added activated polysaccharide (PS) is lost. In addition, inclusion of a chromatographic process for purification of the conjugates from unconjugated PS is required.

The present invention utilizes the characteristic chemical property of hydrazide groups on one reactant to react with aldehyde groups or cyanate esters on the other reactant with an improved conjugate yield of at least sixty percent. With this conjugation efficiency the leftover unconjugated protein and polysaccharide would not need to be removed and thus the purification process of the conjugate product can be limited to diafiltration to remove the by-products of small molecules. The new conjugation reaction can be carried out within one or two days with reactant concentrations between 1 and 25 mg/mL at PS/protein ratios from 1:2 to 3:1, at temperatures between 4 and 40 degrees Centigrade, and in a pH range of 5.5 to 7.4, optimal conditions varying from PS to PS.

Application: Cost effective and efficient manufacturing of conjugate vaccines.

Inventors: Che-Hung Robert Lee and Carl E. Frasch (CBER/FDA)

Patent Status: U.S. Patent Application No. 10/566,899 filed 01 Feb 2006, claiming priority to 06 Aug 2003 (HHS Reference No. E–301–2003/0–US–10); U.S. Patent Application No. 10/566,898 filed 01 Feb 2006, claiming priority to 06 Aug 2003 (HHS Reference No. E–301–2003/1–US–02); International rights available.

Licensing Status: Available for non-exclusive licensing.

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

γPGA Conjugates for Eliciting Immune Responses Directed Against *Bacillus anthracis* and Other Bacilli

Description of Invention: This invention claims immunogenic conjugates of a poly-γ-glutamic acid (γPGA) of *B. anthracis*, or of another bacillus that expresses a γPGA that elicit a serum antibody response against *B. anthracis*, in mammalian hosts to which the conjugates are administered. The invention also relates methods which are useful for eliciting an immunogenic response in mammals, particularly humans, including responses which provide protection against, or reduce the severity of, infections caused by *B. anthracis*. The vaccines claimed in this application are intended for active immunization for prevention of *B. anthracis* infection, and for preparation of immune antibodies. The vaccines of this invention are designed to confer specific immunity against infection with *B. anthracis*, and to induce antibodies specific to *B. anthracis* γPGA. The *B. anthracis* vaccine is composed of non-toxic bacterial components, suitable for infants, children of all ages, and adults.

Inventors: Rachel Schneerson (NICHD), Stephen Leppla (NIAID), John Robbins (NICHD), Joseph Shiloach (NIDDK), Joanna Kubler-Kielb (NICHD), Darrell Liu (NIDCR), Fathy Majadly (NICHD).

Publication: R Schneerson, *et al.* Poly (gamma-D-glutamic acid) protein conjugates induce IgG antibodies in mice to the capsule of *Bacillus anthracis*: a potential addition to the anthrax vaccine. Proc Natl Acad Sci USA. 2003 Jul 22;100(15):8945–50.

Patent Status: U.S. Patent Application No. 10/559,825 filed 02 Dec 2005, claiming priority to 05 Jun 2003 (HHS Reference No. E–343–2002/0–US–04).

Licensing Status: Available for licensing.

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

Oligodeoxynucleotide and its Use To Induce an Immune Response

Description of Invention: This invention comprises oligodeoxynucleotides (ODNs) having at least 10 nucleotides with an unmethylated central CpG motif that are immunostimulatory in humans. The inventors have shown that the various ODNs of this invention (having different CpG motifs and backbones) induce immune responses from human non-B and B cells. The motif that stimulates non-B cells induces production and release of multiple T cell cytokines and chemokines; specifically, the Th1 cytokine IFN-gamma, which facilitates the development of a cytotoxic T cell response. In contrast, the motif that stimulates B cells induces production and release of various cytokines, including, but not limited to IL–6, which supports a Th2 antibody response. The inventors have generated in vitro and ex vivo data showing the ODNs of this invention have utility in precisely regulating the type and magnitude of the immune response in human cells. The present invention has multiple therapeutic uses, including but not limited to cancer, vaccine adjuvants, treating autoimmune disorders and immune system deficiencies, as well as an anti-infective agent and in combination with any antisense therapy.

Inventors: Dennis Klinman (FDA), Daniela Verthelyi (FDA), Kenji Ishii (NINDS).

Patent Status: U.S. Patent Application No. 11/595,211 filed 09 Nov 2006, claiming priority to 12 Apr 1999 (HHS Reference No. E–147–1999/0–US–05).

Licensing Status: Available for licensing.

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

A Method of Immunizing Humans Against Salmonella Typhi Using a Vi-rEPA Conjugate Vaccine

Description of Invention: This invention is a method of immunization against typhoid fever using a conjugate vaccine comprising the capsular polysaccharide of *Salmonella typhi*, Vi, conjugated through an adipic dihydrazide linker to nontoxic recombinant exoprotein A (rEPA) from *Pseudomonas aeruginosa*. The three licensed vaccines against typhoid fever, attenuated *S. typhi* Ty21a, killed whole cell vaccines and Vi polysaccharide, have limited efficacy, in particular for children under 5 years of age, which make an improved vaccine desirable.

It is generally recognized that an effective vaccine against *Salmonella typhi* is one that increases serum anti-Vi IgG eight-fold six weeks after immunization. The conjugate vaccine of the invention increases anti-Vi IgG, 48-fold, 252-fold and 400-fold in adults, in 5–14 years-old and 2–4 years-old children, respectively. Thus this is a highly effective vaccine suitable for children and should find utility in endemic regions and as a traveler's vaccine. The route of administration can also be combined with routine immunization. In 2–5 years old, the protection against typhoid fever is 90% for 4 years. In school age children and in adults the protection could mount to

completer protection according to the immunogenicity data.

Application: Immunization against *Salmonella typhi* for long term prevention of typhoid fever in all ages.

Developmental Status: Conjugates have been synthesized and clinical studies have been performed. The synthesis of the conjugates is described by Kossaczka, *et al.* in Infect Immun. 1997 June;65(7):2088–2093. Phase III clinical studies are described by Mai, *et al.* in N Engl J Med. 2003 October 2; 349(14):1390–1391. Dosage studies are described by Canh, *et al.* in Infect Immun. 2004 Nov; 72(11):6586–6588.

A safety and immunogenicity study in infants are under way. The aim is to administer the conjugate vaccine with routine infant immunization. Preliminary results shows the vaccine is safe in 2 months old infants.

Inventors: Zuzana Kossaczka, Shousun C. Szu, and John B. Robbins (NICHD).

Patent Status: U.S. Patent 6,797,275 issued 28 Sep 2004 (HHS Reference No. E–020–1999/0–US–02); U.S. Patent Application No. 10/866,343 filed 10 Jun 2004 (HHS Reference No. E–020–1999/0–US–03); U.S. Patent Application No. 11/726,304 filed 20 Mar 2007 (HHS Reference No. E–020–1999/0–US–04).

Licensing Status: Available for non-exclusive licensing.

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

Collaborative Research Opportunity: The National Institute of Child Health and Human Development, Laboratory of Developmental and Molecular Immunity, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize A Method of Immunizing Humans Against Salmonella Typhi Using a Vi-rEPA Conjugate Vaccine. Please contact John D. Hewes, Ph.D., at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

Dated: January 10, 2008.

Steven M. Ferguson,

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

[FR Doc. E8–1232 Filed 1–24–08; 8:45 am]

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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.

Diagnosis and Treatment of Barrett's Esophagus and Associated Esophageal Adenocarcinoma

Description of Invention: Barrett's esophagus is a condition in which the normal esophageal tissue lining has been replaced by an abnormal lining of gastric and intestinal tissue resulting from chronic gastroesophageal reflux disease. Patients have an increased risk of developing esophageal adenocarcinoma, which is often detected at later stages and is associated with poor prognosis. Survival rates are very low ranging from 10% in Europe to 16% in the United States.

Available for licensing are microRNA (miRNA) biomarkers that show differential expression in the adenocarcinoma diagnosis and Barrett's esophagus status, and they can predict diagnosis and Barrett's esophagus with accuracies of 71.4% and 74.7%, respectively. Thus, these miRNA biomarkers that may predispose individuals to Barrett's esophagus and/or esophageal adenocarcinoma could provide a means for earlier detection and help in better identifying treatment options.

Applications:

Method to diagnose and treat Barrett's esophagus and esophageal adenocarcinoma.

miRNA pharmaceutical compositions to treat Barrett's esophagus.

Advantages: Early diagnostic that can more accurately stratify patients for increased survival rates and appropriate treatments.

Development Status: The technology is currently in the pre-clinical stage of development.

Market: Esophageal cancer is the 8th most common cancer and 6th most common cause of cancer worldwide.

Survival rate of esophageal cancer is 10% to 16% in Europe and United States respectively.

miRNA technologies have an emerging market, and in 2007, it was worth an estimated 23 million dollars in the U.S. and it has a projected annual growth rate of 100%.

Inventors: Ewy Mathe (NCI), Curtis C. Harris (NCI), *et al.*

Patent Status: U.S. Provisional Application No. 60/979,300 filed 11 Oct 2007 (HHS Reference No. E–008–2008/0–US–01).

Licensing Status: Available for non-exclusive licensing.

Licensing Contact: Jennifer Wong; 301–435–4633; *wongje@mail.nih.gov.*

Collaborative Research Opportunity: The Laboratory of Human Carcinogenesis at the National Cancer Institute is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize methods to diagnose and treat Barrett's esophagus and esophageal carcinoma. Please contact John D. Hewes, Ph.D. at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

Mouse Model for Obesity and Type 2 Diabetes Due to Inactivation of ANKRD26 Gene

Description of Invention: Obesity and type II diabetes are major health hazards both in the United States and internationally. The incidence of obesity has been steadily increasing, underscoring the need to identify and develop effective treatments. As a result, there has been a strong effort to create animal models to help study these diseases.

NIH inventors have created a new mouse model for obesity and type II diabetes. In this model, both copies of the ANKRD26 gene are inactivated by the insertion of a marker gene (beta-galactosidase) into the open reading frame of the gene. The resulting knockout mouse exhibits extreme obesity, increased organ and body size,