

of infection. The potential broad application of these compounds could address a significant health need for effective antivirals.

**Applications:** This technology provides compositions and methods for the treatment of viral infection and has human and veterinary applications.

**Advantages:** The compounds described by the current technology are not necessarily specific for a type of virus or viral strain like many currently available antiviral compounds, and therefore have broad therapeutic antiviral applications. Further, virions resistant to damage by antibody and complement have been shown to be lysed by compounds of the invention suggesting antiviral surveillance independent of a humoral immune response.

**Development Status:** Proof of concept in vitro studies using human cells have shown antiviral activity with viruses pseudotyped with envelope proteins from Ebola, HIV, Marburg and MoMuLV.

**Inventors:** Gary Nabel and Jae-Ouk Kim (VRC/NIAD).

**Publication:** J-O Kim *et al.* Lysis of human immunodeficiency virus type 1 by a specific secreted human phospholipase A<sub>2</sub>. *J Virol.* 2007 Feb;81(3):1444–1450.

**Patent Status:** PCT Application No. PCT/US2007/004471 filed 21 Feb 2007 (HHS Reference No. E-013-2006/1-PCT-01).

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

**Licensing Contact:** Susan Ano, Ph.D.; 301/435-5515; [AnoS@mail.nih.gov](mailto:AnoS@mail.nih.gov)

### Design of Multi-Functional RNA Nanoparticles and Nanotubes

**Description of Invention:** The characteristic function of nanoparticles is their ability to deliver drug across biological barriers to the target site while protecting the drugs from the biological environment until they reach the target site. The present invention provides polyvalent RNA nanostructures comprising RNA I inverse (RNA Ii) or RNA II inverse (RNA Iii) like motifs that have multiple positions available for conjugation of therapeutic, diagnostic or delivery agents. The nanoparticles of the invention do not induce significant immune response by themselves and are smaller than currently available nanoparticles and therefore allow for increased efficiency of administration. The nanoparticles of this invention have the ability to deliver one or more different therapeutic agents in a single particle. Further, the RNA nanoparticles are also capable of self-assembly into

nanotubes of various shapes which offer potentially broad uses in medical implants, gene therapy, nanocircuits, scaffolds and medical testing.

#### Applications:

1. Use as diagnostic tool.
2. Use as drug delivery composition to treat various diseases or conditions.
3. Use in screening or identifying potential chemotherapeutic agents.
4. Use in riboswitch aptamers, ribozymes or beacons.
5. Use in nanocircuits, medical implants, gene therapy, scaffolds and medical testing.

**Market:** Broad application in various fields, such as therapeutics, drug delivery, diagnostics, provides a wide market potential.

**Development Status:** Early stage.

**Inventors:** Bruce A. Shapiro and Yaroslava G. Yingling (NCI).

**Publication:** YG Yingling and BA Shapiro. Computational Design of an RNA Hexagonal Nanoring and an RNA Nanotube. *Nano Lett.* 2007 Jul 6. Epub ahead of print, doi 10.1021/nl070984r.

**Patent Status:** U.S. Provisional Application No. 60/810,283 filed 02 Jun 2006 (HHS Reference No. E-233-2006/0-US-01).

U.S. Provisional Application No. 60/918,181 filed 14 Mar 2007 (HHS Reference No. E-233-2006/1-US-01).

**Licensing Status:** Available for exclusive and non-exclusive licensing.

**Licensing Contact:** Robert M. Joynes J.D., M.S.; 301/594-6565; [joynesr@mail.nih.gov](mailto:joynesr@mail.nih.gov).

**Collaborative Research Opportunity:** The National Cancer Institute's Nanobiology Program (<http://www-lecb.ncifcrf.gov/bshapiro/index.html>) is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize RNA nanostructures. Please contact John D. Hewes, Ph.D. at 301-435-3121 or [hewesj@mail.nih.gov](mailto:hewesj@mail.nih.gov) for more information.

### Methods for Preparing Complex Multivalent Immunogenic Conjugates

**Description of Technology:** 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](mailto:soukasp@mail.nih.gov).

Dated: August 13, 2007.

**Steven M. Ferguson,**

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

[FR Doc. E7-16400 Filed 8-20-07; 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.

### Methods of Glycosylation and Bioconjugation

**Description of Technology:** Eukaryotic cells express several classes of oligosaccharides attached to proteins or lipids. Animal glycans can be N-linked via beta-GlcNAc to Asn (N-glycans), O-linked via -GalNAc to Ser/Thr (O-glycans), or can connect the carboxyl end of a protein to a phosphatidylinositol unit (GPI-anchors) via a common core glycan structure. Beta (1,4)-galactosyltransferase I catalyzes the transfer of galactose from the donor, UDP-galactose, to an acceptor, N-acetylglucosamine, to form a galactose-beta (1,4)-N-acetylglucosamine bond, and allows galactose to be linked to an N-acetylglucosamine that may itself be linked to a variety of other molecules. Examples of these molecules include other sugars and proteins. The reaction can be used to make many types of molecules having great biological significance. For example, galactose-beta (1,4)-N-acetylglucosamine linkages are important for many recognition events that control how cells interact with each other in the body, and how cells interact with pathogens. In addition, numerous other linkages of this type are also very important for cellular recognition and binding events as well as cellular interactions with pathogens, such as viruses. Therefore, methods to synthesize these types of bonds have many applications in research and medicine to develop pharmaceutical agents and improved vaccines that can be used to treat disease.

The invention provides *in vitro* folding method for a polypeptidyl-alpha-N-acetylgalactosaminyltransferase (pp-GalNAc-T) that transfers GalNAc to Ser/Thr residue on a protein. The application claims that this *in vitro*-folded recombinant ppGalNAc-T enzyme transfers modified sugar with a chemical handle to a specific site in the designed C-terminal polypeptide tag fused to a protein. The invention

provides methods for engineering a glycoprotein from a biological substrate, and methods for glycosylating a biological substrate for use in glycoconjugation. Also included in the invention are diagnostic and therapeutic uses.

**Application:** Enzymes and methods are provided that can be used to promote the chemical linkage of biologically important molecules that have previously been difficult to link.

**Developmental Status:** Enzymes have been synthesized and characterization studies have been performed.

**Inventors:** Pradman Qasba and Boopathy Ramakrishnan (NCI/SAIC).

**Patent Status:** U.S. Provisional Application No. 60/930,294 filed 14 May 2007 (HHS Reference No. E-204-2007/0-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](mailto:soukasp@mail.nih.gov).

**Collaborative Research Opportunity:** The National Cancer Institute is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize this technology. Please contact John D. Hewes, Ph.D. at 301-435-3121 or [hewesj@mail.nih.gov](mailto:hewesj@mail.nih.gov) for more information.

### Improved Bacterial Host for Production of Anthrax Toxin Proteins and Vaccines: *Bacillus anthracis* BH450

**Description of Invention:** Anthrax toxin has previously been made from various avirulent strains of *Bacillus anthracis*. The inventors have genetically engineered a new strain of *B. anthracis* with improved properties. The strain, designated BH450, is totally deficient in the ability to make spores and to produce a major extracellular protease designated Peptidase M4. The genetic lesions introduced are defined, true deletions, so there is no possibility of reversion. Inability to make spores assures that laboratories growing the strain will not become contaminated with the very stable anthrax spores. Inability to make peptidase M4 increases the stability of proteins such as anthrax toxin that are secreted to the culture medium.

**Applications and Modality:** *B. anthracis* vaccine/prophylactic and therapeutic studies.

**Market:** Research tool useful for biodefense/therapeutic studies.

**Development Status:** The technology is a research tool.

**Inventors:** Andrei Pomerantsev, Dana Hsu, Ramakrishnan Sitaraman, Craig

Galloway, Violetta Kivovich, Stephen Leppla (NIAID).

**Publication:** AP Pomerantsev *et al.* Genome engineering in *Bacillus anthracis* using Cre recombinase. *Infect Immun.* 2006 Jan;74(1):682-693.

**Patent Status:** HHS Reference No. E-127-2007/0—Research Tool.

**Licensing Status:** This technology is not patented. The strain will be transferred through a Biological Materials License.

**Licensing Contact:** Peter A. Soukas, J.D.; 301/435-4646; [soukasp@mail.nih.gov](mailto:soukasp@mail.nih.gov).

**Collaborative Research Opportunity:** The National Institute of Allergy and Infectious Diseases, Laboratory of Bacterial Diseases, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize *Bacillus anthracis* BH450 strain. Please contact Dr. Andrei P. Pomerantsev at phone 301-451-9817 and/or e-mail [apomerantsev@niaid.nih.gov](mailto:apomerantsev@niaid.nih.gov) for more information.

### Compositions and Methods for Increasing Recombinant Protein Yields Through the Modification of Cellular Properties

**Description of Technology:** This technology relates to compositions and methods for improving the growth characteristics of cells engineered to produce biologically active products such as antibodies or glycosylated proteins. Featured is a method that uses gene candidates (e.g., *cdkl3*, *siat7e*, or *lama4*), or their expressed or inhibited products in cell lines, such as Human Embryonic Kidney (including HEK-293), HeLa, or Chinese Hamster Ovary (CHO). The gene expression modulates growth characteristics, such as adhesion properties, of the cell lines thereby increasing recombinant protein yields and reducing product production costs.

**Applications:** This technology may be used to improve production of therapeutic and/or diagnostic compounds, including therapeutic proteins or monoclonal antibodies from mammalian cells. Optimization of mammalian cells for use as expression systems in the production of biologically active products is very difficult. For certain applications, anchorage-independent cell lines may be preferred, whereas for other applications, a cell line that adheres to a surface, e.g. is anchorage-dependent, may be preferable. This technology provides a method for identifying a gene whose expression modulates such cellular adhesion characteristics. This method thus leads to an increase in the

expression or yield of polypeptides, including therapeutic biologicals, such as antibodies, cytokines, growth factors, enzymes, immunomodulators, thrombolytics, glycosylated proteins, secreted proteins, and DNA sequences encoding such polypeptides and a reduction in the associated costs of such biological products.

**Advantages:** This technology offers the ability to improve yields and reduce the cost associated with the production of recombinant protein products through the selection of cell lines having: altered growth characteristics; altered adhesion characteristics; altered rate of proliferation; improvement in cell density growth; improvement in recombinant protein expression level.

**Market:** Biopharmaceuticals, including recombinant therapeutic proteins and monoclonal antibody-based products used for in vivo medical purposes and nucleic acid based medicinal products now represent approximately one in every four new pharmaceuticals on the market. The market size has been estimated at \$33 billion in 2004 and is projected to reach \$70 billion by the end of the decade. The list of approved biopharmaceuticals includes recombinant hormones and growth factors, mAB-based products and therapeutic enzymes as well as recombinant vaccines and nucleic acid based products.

Mammalian cells are widely used expression systems for the production of biopharmaceuticals. Human embryo kidney (including HEK-293) and Chinese hamster ovary (CHO) are host cell of choice. The genes identified in this technology (e.g., cdk13, sia7e, or lama4) can be used to modify these important cell based systems.

This technology is ready for use in drug/vaccine discovery, production and development. The technology provides methods for identification of specific gene targets useful for altering the production properties of either existing cell lines to improve yields or with new cell lines for the production of therapeutic and or diagnostic compounds from mammalian cells.

Companies that are actively seeking production platforms based on mammalian cell lines that offer high efficiency, high throughput systems for protein production or analysis at lower cost and ease of scale-up would be potential licensors of this technology.

**Development Status:** Late Stage—Ready for Production.

**Inventors:** Joseph Shiloach (NIDDK), Pratik Jaluria (NIDDK).

**Related Publication:** P. Jaluria *et al.* Application of microarrays to identify and characterize genes involved in

attachment dependence in HeLa cells. *Metab Eng.* 2006 Dec 13, Epub ahead of print, doi:10.1016/j.ymben.2006.12.001.

**Patent Status:** U.S. Provisional Application No. 60/840,381 filed 24 Aug 2006 (HHS Reference No. E-149-2006/0-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](mailto:soukasp@mail.nih.gov).

**Collaborative Research Opportunity:** The National Institute of Diabetes and Digestive and Kidney Diseases, Biotechnology Core Laboratory, is seeking parties interested in collaborative research projects directed toward the use of this technology with cells for drug and vaccine production and development, including growth optimization, production and product recovery processes. For more information, please contact Dr. Joseph Shiloach, [josephs@intra.niddk.nih.gov](mailto:josephs@intra.niddk.nih.gov), or Rochelle S. Blaustein at [Rochelle.Blaustein@nih.gov](mailto:Rochelle.Blaustein@nih.gov).

#### **Methods for Conjugation of Oligosaccharides or Polysaccharides to Protein Carriers Through Oxime Linkages Via 3-Deoxy-D-Manno-Octulosonic Acid**

**Description of Technology:** This technology comprises new methods for the conjugation of O-specific polysaccharides/oligosaccharides (O-SP/OS) derived from bacterial lipooligosaccharides/lipopolysaccharides (LOS/LPS), after their cleavage from Lipid A, to carrier proteins, to serve as potential vaccines. Conjugation is performed between the carbonyl group on the terminal reducing end of the saccharide and the aminoxy group of a bifunctional linker bound further to the protein.

The inventors have carried out the reaction under mild conditions and in a short time resulting in binding 3-deoxy-D-manno-octulosonic acid (KDO) on the saccharide to the protein. These conjugates preserve the external non-reducing end of the saccharide, are recognized by antisera, and induce immune responses in mice to both conjugate components (i.e., the OS and the associated carrier protein).

**Application:** Cost effective and efficient manufacturing of conjugate vaccines.

**Inventors:** Joanna Kubler-Kielb (NICHHD), Vince Pozsgay (NICHHD), Gil Ben-Menachem (NICHHD), Rachel Schneerson (NICHHD), *et al.*

**Patent Status:** U.S. Provisional Application No. 60/832,448 filed 21 Jul 2006 (HHS Reference No. E-183-2005/0-US-01); PCT Patent Application filed

21 Jul 2007 (HHS Reference No. E-183-2005/0-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](mailto:soukasp@mail.nih.gov).

#### **In Vitro Model for Hepatitis C Virion Production**

**Description of Technology:** This invention provides an in vitro hepatitis C virus (HCV) replication system that is capable of producing viral particles in a culture medium. Hepatitis C is a major public health problem, the development of therapeutics for which has been hampered by a lack of a robust model system to study the complete viral life cycle. This invention provides a new model system for the complete replication cycle of hepatitis C virus and virion production, assembly and release. The model is useful for screening antiviral agents against HCV.

A full length HCV construct, CG1b of genotype 1b which is known to be infectious, was placed between two ribozymes designed to generate the exact 5' and 3' ends of HCV when cleaved. Using this system, HCV proteins and positive and negative RNA strands have been shown to reproduce intracellularly, and viral particles that resemble authentic HCV virions are produced and secreted into the culture medium.

The patent application includes claims directed toward the following: A construct comprising specific nucleic acid sequences including HCV genotype 1b, genotype 1a, genotype 2a or potentially other genotypes; a method for identifying a cell line that is permissive for infection with HCV; a method for propagating HCV in vitro; a method for screening agents capable of modulating HCV replication or activity; a method for testing the level of HCV replication or activity; a HCV vaccine comprising HCV virus particles.

**Applications:** The model offers a novel method for investigating the entire HCV life cycle including replication and pathogenesis and is useful for high-throughput antiviral screening. This technique may also be useful for making infectious particles that are useful in the production of HCV vaccines.

**Advantages:** This system provides a new, stable and efficient cell culture model to further study the life cycle and biology of HCV, and to test potential therapeutic targets for hepatitis C. This model has also been used to generate in cell culture HCV strains infectious for chimpanzees, the only experimental animal susceptible to infection with the

hepatitis C virus, a critical step in the development of new vaccines for Hepatitis C.

**Market:** Hepatitis C virus (HCV) chronically infects approximately 200 million people worldwide and increases the risk of developing cirrhosis and hepatocellular carcinoma. This technology would be useful for studying the HCV life cycle, screening for therapeutic agents against multiple HCV strains, including Genotype 1a, 1b and 2a, and the development of HCV vaccines. HCV genotypes 1 and 2 are the major genotypes with worldwide distribution; they are known to be associated with different clinical profiles and therapeutic responses. Hence, the model may be used to screen for varying levels of effectiveness of therapeutics against the major HCV genotypes.

**Development Status:** This technology is available for use in diagnostics, drug/vaccine discovery, production and development. Current work is directed toward studies into the HCV life cycle and replication and the pathogenesis of HCV screening for antiviral agents against multiple HCV strains. This model has been used to generate in cell culture HCV strains infectious for chimpanzees, the only experimental animal susceptible to infection with the hepatitis C virus, a critical step in the development of new vaccines for Hepatitis C. Future work may be directed toward the use of this system for development of vaccine candidates against HCV.

**Inventors:** T. Jake Liang and Theo Heller (NIDDK).

**Related Publications:**

1. Z. Hu *et al.* Altered proteolysis and global gene expression in hepatitis B virus X transgenic mouse liver. *J Virol.* 2006 Feb;80(3):1405–1413.

2. T. Heller *et al.* An *in vitro* model of hepatitis C virion production. *Proc Natl Acad Sci USA.* 2005 Feb 15;102(7):2579–2583.

**Patent Status:** PCT Application No. PCT/US2005/035487 filed 30 Sep 2005 (HHS Reference No. E–324–2004/3–PCT–01), based on: U.S. Provisional Application No. 60/615,301 filed 30 Sep 2004 (HHS Reference No. E–324–2004/0–US–01), now abandoned; U.S. Provisional Application No. 60/642,210 filed 06 Jan 2005 (HHS Reference No. E–324–2004/1–US–01), now abandoned; U.S. Provisional Application No. 60/720,692 filed 26 Sep 2005 (HHS Reference No. E–324–2004/2–US–01), now abandoned.

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

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

**Collaborative Research Opportunity:** The National Institute of Diabetes and Digestive and Kidney Diseases, Liver Diseases Branch, is seeking parties interested in collaborative research directed toward molecular strategies for vaccine and antiviral development, and animal models of viral hepatitis C. Please contact Dr. T. Jake Liang at 301–496–1721, [jiang@nih.gov](mailto:jiang@nih.gov) or Rochelle S. Blaustein at [Rochelle.Blaustein@nih.gov](mailto:Rochelle.Blaustein@nih.gov) for more information.

**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](mailto: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 Technology:** 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](mailto:soukasp@mail.nih.gov).

### Neutralizing Monoclonal Antibodies to Respiratory Syncytial Virus

*Description of Technology:* Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia among infants and children under 1 year of age. Illness begins most frequently with fever, runny nose, cough, and sometimes wheezing. During their first RSV infection, between 25% and 40% of infants and young children have signs or symptoms of bronchiolitis or pneumonia, and 0.5% to 2% require hospitalization. Most children recover from illness in 8 to 15 days. The majority of children hospitalized for RSV infection are under 6 months of age. RSV also causes repeated infections throughout life, usually associated with moderate-to-severe cold-like symptoms; however, severe lower respiratory tract disease may occur at any age, especially among the elderly or among those with compromised cardiac, pulmonary, or immune systems.

This invention is a human monoclonal antibody fragment (Fab) discovered utilizing phage display technology. The neutralizing monoclonal antibody was isolated and its binding site was identified. Fab F2-5 is a broadly reactive fusion (F) protein-specific recombinant Fab generated by antigen selection from a random combinatorial library displayed on the surface of filamentous phage. In an in vitro plaque-reduction test, the Fab RSVF2-5 neutralized the infectivity of a variety of field isolates representing viruses of both RSV subgroups A and B. The Fab recognized an antigenic determinant that differed from the only other human anti-F monoclonal antibody (RSV Fab 19) described thus far. A single dose of 4.0 mg of Fab RSVF2-5/kg of body weight administered by inhalation was sufficient to achieve a 2000-fold reduction in pulmonary virus titer in

RSV-infected mice. The antigen-binding domain of Fab RSVF2-5 offers promise as part of a prophylactic regimen for RSV infection in humans.

*Application:* Respiratory Syncytial Virus prophylaxis/therapeutic.

*Development Stage:* The antibodies have been synthesized and preclinical studies have been performed.

*Inventors:* Brian Murphy (NIAID), Robert Chanock (NIAID), James Crowe (NIAID), *et al.*

*Publication:* JE Crowe *et al.* Isolation of a second recombinant human respiratory syncytial virus monoclonal antibody fragment (Fab RSVF2-5) that exhibits therapeutic efficacy in vivo. *J Infect Dis.* 1998 Apr;177(4):1073-1076.

*Patent Status:* HHS Reference No. E-001-1996/0—U.S. and Foreign Rights Available.

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

*Licensing Contact:* Peter A. Soukas, JD; 301/435-4646; [soukasp@mail.nih.gov](mailto:soukasp@mail.nih.gov).

### Human Neutralizing Monoclonal Antibodies to Respiratory Syncytial Virus and Human Neutralizing Antibodies to Respiratory Syncytial Virus

*Description of Technology:* This invention is a human monoclonal antibody fragment (Fab) discovered utilizing phage display technology. It is described in Crowe *et al.*, *Proc Natl Acad Sci USA.* 1994 Feb 15;91(4):1386-1390 and Barbas *et al.*, *Proc Natl Acad Sci USA.* 1992 Nov 1;89(21):10164-10168. This MAb binds an epitope on the RSV F glycoprotein at amino acid 266 with an affinity of approximately  $10^9 M^{-1}$ . This MAb neutralized each of 10 subgroup A and 9 subgroup B RSV strains with high efficiency. It was effective in reducing the amount of RSV in lungs of RSV-infected cotton rats 24 hours after treatment, and successive treatments caused an even greater reduction in the amount of RSV detected.

*Applications:* Research and drug development for treatment of respiratory syncytial virus.

*Inventors:* Robert M. Chanock (NIAID), Brian R. Murphy (NIAID), James E. Crowe Jr. (NIAID), *et al.*

*Patent Status:* U.S. Patent 5,762,905 issued 09 June 1998 (HHS Reference No. E-032-1993/1-US-01); U.S. Patent 6,685,942 issued 03 February 2004 (HHS Reference No. E-032-1993/1-US-02); U.S. Patent Application No. 10/768,952 filed 29 January 2004 (HHS Reference No. E-032-1993/1-US-03).

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

*Licensing Contact:* Peter A. Soukas, JD; 301/435-4646; [soukasp@mail.nih.gov](mailto:soukasp@mail.nih.gov).

### Murine Monoclonal Antibodies Effective To Treat Respiratory Syncytial Virus

*Description of Technology:* Available for licensing through a Biological Materials License Agreement are the murine MAbs described in Beeler *et al.*, "Neutralization epitopes of the F glycoprotein of respiratory syncytial virus: effect of mutation upon fusion function," *J Virol.* 1989 July;63(7):2941-2950. The MAbs that are available for licensing are the following: 1129, 1153, 1142, 1200, 1214, 1237, 1112, 1269, and 1243. One of these MAbs, 1129, is the basis for a humanized murine MAb (see U.S. Patent 5,824,307 to humanized 1129 owned by MedImmune, Inc.), recently approved for marketing in the United States. MAbs in the panel reported by Beeler *et al.* have been shown to be effective therapeutically when administered into the lungs of cotton rats by small-particle aerosol. Among these MAbs several exhibited a high affinity (approximately  $10^9 M^{-1}$ ) for the RSV F glycoprotein and are directed at epitopes encompassing amino acids 262, 272, 275, 276 or 389. These epitopes are separate, nonoverlapping and distinct from the epitope recognized by the human Fab of U.S. Patent 5,762,905 owned by The Scripps Research Institute.

*Applications:* Research and drug development for treatment of respiratory syncytial virus.

*Inventors:* Robert M. Chanock, Brian R. Murphy, Judith A. Beeler, and Kathleen L. van Wyke Coelingh (NIAID).

*Patent Status:* HHS Reference No. B-056-1994/1—Research Tool.

*Licensing Status:* Available for non-exclusive licensing under a Biological Materials License Agreement.

*Licensing Contact:* Peter A. Soukas, JD; 301/435-4646; [soukasp@mail.nih.gov](mailto:soukasp@mail.nih.gov).

Dated: August 13, 2007.

**Steven M. Ferguson,**

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

[FR Doc. E7-16401 Filed 8-20-07; 8:45 am]

**BILLING CODE 4140-01-P**