Anti-γ-H2A Antibody and Method for Detecting DNA Double-Stranded Breaks

William M. Bonner, Efthimia P. Rogakou (NCI)
Serial No. 09/351,721 filed 12 Jul 1999

There presently exist assays for determining DNA breakage due to stresses such as radiation and toxins. These include the TUNEL assay and single cell gel electrophoresis, among others. The difficulty in using these and other assays arises in that a great number of DNA breaks are necessary for adequate detection of the breakage. Since only 40 double-stranded breaks in the DNA leads to cell death, it is evident that there is a need for an assay with greater specificity.

The NIH announces a new technology which relates to such an improvement over current DNA detection assays, with the ability to be sensitive enough to detect a single DNA double-stranded break in a cell's nucleus. This method for detection uses antibodies directed against a synthetic phosphorylated peptide containing the mammalian γ-H2AX C-terminal sequence for deletion of DNA double-stranded breaks. It centers on the activity of the H2A histone. In response to a DNA break, H2A can become phosphorylated in great numbers and provide protection for the break site to assist in repair. The antibody and method available show specificity for this occurrence and thus allow detection at levels much lower than are presently needed by other detection techniques. Use of such technology could be widespread, both as a diagnostic tool and with specific DNA breakage-related disease and syndrome research.

Dated: August 29, 2000.

Jack Spiegel,

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

[FR Doc. 00–22881 Filed 9–6–00; 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, DHHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by agencies 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.

A High Yield Pertussis Vaccine Production Strain and Method for Making Same

Tod J. Merkel, Jerry M. Keith and Xiaoming Yang (NIDCR)
DHHS Reference No. E–159–99/0 filed 26 Jun 2000
Licensing Contact: Uri Reichman; 301/496–7736 ext. 240; e-mail: reichmau@od.nih.gov

Pertussis Toxin (PT) in its chemically detoxified forms has emerged as the most promising acellular vaccine against *Bordetella pertussis (B. pertussis),* the organism responsible for whooping cough. Genetically detoxified forms of PT have recently been demonstrated as potential vaccine candidates against this organism, and may offer the advantages of enhanced stability and ease of manufacturing. The need for production of large quantities of PT and its genetically detoxified forms keeps growing, but the current methods of production of the toxin from *B. pertussis* have proven to be rather cumbersome and inefficient, resulting in poor yields and impure form of the desired protein. The present invention provides for a new way to circumvent these difficulties and renders the process more amenable to industrial needs. The present invention describes the development of a new genetically engineered strain of *Bordetella bronchiseptica,* named BBPT, which grows at a high rate relative to *B. pertussis,* and is capable of producing wild type or genetically detoxified form of PT in pure form, with high yields and in a cost effective fashion. The high degree of purity of the product is achieved due to the knockout of the filamentous hemagglutinin (FHA) gene in this new strain. The presence of the FHA protein, which is inherent in the conventional methods of production, requires extra purification steps, thus resulting in poor and inconsistent yields of the toxin. The BBPT strain of the present invention may play a major role in the acceleration of programs dedicated to the development of improved and efficacious vaccines against *B. pertussis.*

Activation of Antigen Presenting Cells to Respond To a Selected Antigen

Polly Matzinger, Stefania Gallucci, Martijn Lolkema (NIAID)
DHHS Reference No. E–018–00/0 filed 25 Oct 1999
Licensing Contact: Peter Soukas; 301/496–7056 ext. 268; e-mail: soukasp@od.nih.gov

The inventors have found that alpha interferon and the supernatant of necrotic cells can act as adjuvants when co-injected along with a protein, such as OVA, to initiate a primary *in vivo* immune response in mice. The compositions of the present invention can induce dendritic cells to activate and become good Antigen Presenting Cells (APCs) and consequently initiate an immune response. The advantage of these adjuvants is that they are more physiological and they allow for repeated vaccination, which current adjuvant technology makes difficult due to the side effects of the adjuvants. The invention also provides uses and applications for the adjuvants, including, but not limited to, transplant rejection, spontaneous tumor rejection, some forms of spontaneous abortion, and some forms of autoimmunity. The invention is further described in Nature Medicine 1999 Nov; 5(11):1249–55.

Dated: August 29, 2000.

Jack Spiegel,

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

[FR Doc. 00–22882 Filed 9–6–00; 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, DHHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by agencies 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 Uri Reichman, Ph.D., at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7736 ext. 240; fax: 301/402–0220; e-mail: reichmau@od.nih.gov. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Use of Recombinant Parainfluenza Viruses (PIVs) as Vectors To Protect Against Infection and Disease Caused by PIV and Other Human Pathogens

B. Murphy, P. Collins, A. Durbin, M. Skiadopoulos and T. Tao (NIAID)
DHHS Reference No. E–099–99/0 filed 10 Dec 1999

The invention relates to the design and creation of recombinant chimeric parainfluenza viruses, novel vaccine candidates against PIV and non-PIV pathogens. The chimeric viruses utilize the PIV genome as a carrier/vector for heterologous PIV or non-PIV genes that code for the protective antigens of the pathogens. For example, the glycoproteins genes of PIV1 and PIV2 can be incorporated into PIV3 genome, either substituting for or in addition to the vector's glycoprotein genes. The latter design can serve as a single vaccine against the three types of PIV pathogens. Furthermore, PIV can serve as a carrier for the ''protective'' genes of non-PIV pathogens such as measles, RSV, mumps, herpes, influenza and more. In this design, again, the ''donor'' genes can substitute for or be added to the vector's protecting genes. The latter design can serve as a single vaccine against plurality of pathogens. In particular, the invention describes the potential benefit of developing new vaccine candidates against the measles virus.

The live attenuated measles virus currently in commercial use must be administered by intramuscular injection, and cannot be given until 12 months of age due to neutralization by maternal antibodies present in young infants. There is a strong need to develop a vaccine which will be effective in the first year of life. A chimeric PIV3-measles vaccine described in this invention has shown to confer protection against the two pathogens. Initial studies indicate that this vaccine candidate will be able to circumvent the difficulties encountered by the currently licensed vaccine, i.e., it will be possible to administer the vaccine by intranasal route so that it will be effective in the presence of maternal antibodies. This vaccine will make it possible, for the first time, to immunize young infants against the deadly measles virus.

Attenuated Human-Bovine Chimeric Parainfluenza Virus (PIV) Vaccines

M. Skiadopoulos, P. Collins, B. Murphy and A. Schmidt (NIAID)
DHHS Reference No. E–201–00/0 filed 05 Jul 2000

The invention relates to the engineering and creation of recombinant chimeric human-bovine parainfluenza viruses (PIVs) and novel vaccine candidates against PIV. The chimera of the invention include a partial or complete ''background'' PIV genome or antigenome derived from or patterned after a bovine PIV virus, combined with one or more heterologous gene(s) or genome segment(s) of a human PIV virus to form a human-bovine chimeric PIV genome or antigenome. The inverted design is also possible, where the chimeric PIV incorporates a partial or complete human PIV ''background'' genome or antigenome, combined with one or more heterologous gene(s) or genome segment(s) from bovine PIV, whereby the resultant chimeric virus is attenuated by virtue of the host-range restriction specified by the bovine genes. In particular, the invention describes the creation of chimera where the human PIV HN and F ''protective'' genes are incorporated into a bovine ''background'' genome, and another one where bovine PIV3 P and M open reading frames replace that of human in a human PIV3 ''background'' genome. The vaccine candidates created by this recombinant technique can be further attenuated by incorporating specific point mutations and nucleotide modifications into the genome to yield desired phenotypic and structural effects.

Respiratory Syncytial Virus Vaccines Expressing Protective Antigens From Promoter-Proximal Genes

C. Krempl, P. Collins, B. Murphy, U. Buchholz and S. Whitehead (NIAID)
DHHS Reference No. E–225–00/0 filed 23 Jun 2000

The invention relates to the engineering and creation of novel live-attenuated RSV vaccine candidates. The viruses of this invention have been modified by shifting the position of one or more of various viral genes relative to the viral promoter. The gene-shifted RSVs are constructed by insertion, deletion and rearrangement of genes or genome segments within the recombinant genome or antigenome. Shifting the position of the gene(s) in this manner provides for a selective increase or decrease in expression of the gene(s), depending on the nature and degree of the positional shift. Genes of interest for manipulation to create gene position-shifted RSV include any of the NS1, NS2, N, P, M, SH, M2(ORF1), M2(ORF2), L, F or G genes or genome segment.

One modification of particular interest is to place the G and F protective antigen genes in a promoter-proximal position for increased expression. The gene position-shifted RSV can be further manipulated by the addition of specific nucleotide and amino acid point mutations or host range restriction determinants to yield desired phenotypic and structural effects. This technique offers the possibility of producing a vaccine that is ''better than nature'' by increasing the relative expression of particular genes.

Multiple Hybridization System for the Identification of Pathogenic *Mycobacterium* Species and Method of Use

Steven Fischer, Gary Fahle, Patti Conville and Jang Rampall (CC)
DHHS Reference No. E–278–99/0 filed 03 March 2000

The invention relates to a multiplex system that allows simultaneous detection and identification of any one of six different species of mycobacteria, *M. gordonae, M. intracellulare, M. avium, M. tuberculosis, M. marinum,* or *M. kansasii*. The *Mycobacterium* species included in this detection system, collectively, constitute about 90% of the patient isolates detected in many clinical mycobacteriology lab sections. The system includes primers and amplification reagents that, when applied to the clinical specimen can generate detection oligonucleotide for the *Mycobacterium* species, in one step and in a single tube. The system also includes a plastic device comprising an array of the corresponding capture oligonucleotides of known sequences. Upon generating the amplified detection probes, the detection mixture is applied to the plastic device for hybridization to take place. Following a wash step, the hybridized locations on the array are detected by fluorescence or chemiluminescence to determine which of the six possible *Mycobacterium* species are present in the sample. The system is simple to operate and permits the identification of these six

mycobacteria in patient samples in a single day.

Method of Diagnosing Multidrug Resistant Tuberculosis

Clifton E. Barry, III, Andrea E. DeBarber, Khisimuzi Mdluli and Linda-Gail Bekker (NIAID)

DHHS Reference No. E–093–00/0 filed 26 Jun 2000

The invention relates to the discovery that a putative gene of *Mycobacterium tuberculosis* (*MTb*) with no previously identified function is responsible for the ability of the bacteria to activate a class of second line thioamide drugs used for *MTb* infections. The gene, termed ''*etaA*'', codes for the synthesis of a monooxigenase, the enzyme responsible for the oxidative activation of the drugs. Mutation in the *etaA* gene leads to the expression of mutated, inactivated enzyme, thus resulting in thioamide drug-resistant bacteria. The significance of this discovery is that now, resistance to the class of thioamide drugs in clinical isolates can be identified in a relatively short time, eliminating the need to perform lengthy culturing procedures. The invention claims test methods for determining resistance to thioamide drugs by detecting gene mutation. These include (a) amplifying the *etaA* gene or a portion of it containing the mutation, with a set of primers which provide amplified product, and sequencing the amplified product to compare the sequence with a known sequence of the wild-type *etaA*. A difference in sequence patterns indicate mutation, (b) subjecting the amplified gene product to digestion by restriction enzymes and comparing the cleaved DNA gel pattern to the one obtained from digestion of the wild type *etaA* gene. A difference indicates mutation in *etaA*, and (c) detecting the mutations by probe hybridization techniques, where the amplified product hybridizes to a nucleic acid of known sequence under stringent conditions, and the hybridized product is detected. In addition to the above, the invention proposes other detection methods such as commonly used for SNPs. Other methods claimed in the invention are immunoassay (*i.e.* ELISA) for the *etaA* gene product or mutated versions of it, or immunoassay and chemical analysis of the drug metabolites, whereby the absence of the metabolites indicates gene mutation and impaired activating ability.

Dated: August 29, 2000.

Jack Spiegel,

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

[FR Doc. 00–22883 Filed 9–6–00; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes Health

National Center for Research Resources; Notice of Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meeting.

The meeting will be open to the public as indicated below, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should notify the Contact person listed below in advance of the meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552(c)94) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Center for Research Resources Initial Review Group, General Clinical Research Centers Review Committee.

Date: October 11–12, 2000.

Open: October 11, 2000, 8 AM to 9:30 AM.

Agenda: To discuss program planning and program accomplishments.

Place: Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, MD 20814.

Close: October 11, 2000,, 9:30 AM to Adjournment.

Agenda: To review and evaluate grant applications.

Place: Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, MD 20814.

Contact Person: John L. Meyer, PhD, Deputy Director, Office of Review, National Center for research Resources, National Institutes of Health, One Rockledge Centre, Suite 6018, 6705 Rockledge Drive, Msc 7965, Bethesda, MD 20892–7965, 301–435–0806.

(Catalogue of Federal Domestic Assistance Program Nos. 93.306, Comparative Medicine, 93.306, Clinical Research, 93.333; 93.371, Biomedical Technology; 93.389, Research Infrastructure, National Institutes of Health, HHS)

Dated: August 30, 2000.

Anna Snouffer,

Acting Director, Office of Federal Advisory Committee Policy.

[FR Doc. 00–22872 Filed 9–6–00; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Center for Research Resources; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Center for Research Resources Special Emphasis Panel Biomedical Research Technology.

Date: October 26, 2000.

Time: 8:00 AM to Adjournment.

Agenda: To review and evaluate grant applications.

Place: Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, MD 20814.

Contact Person: Rebecca A. Fuldner, PHD, Scientific Review Administrator, Office of Review, National Center for Research Resources, 6705 Rockledge Drive, MSC 7965, Room 6018, Bethesda, MD 20892–7965, (301) 435–0809.

(Catalogue of Federal Domestic Assistance Program Nos. 93.306, Comparative Medicine, 93.306; 93.333, Clinical Research, 93.333; 93.371, Biomedical Technology; 93.389, Research Infrastructure, National Institutes of Health, HHS)

Dated: August 30, 2000.

Anna Snouffer,

Acting Director, Office of Federal Advisory Committee Policy.

[FR Doc. 00–22873 Filed 9–6–00; 8:45 am]

BILLING CODE 4140–01–M