Licensing Contact: Richard Rodriguez; 301/496–7056 ext. 287; e-mail: rodrigur@od.nih.gov

The present invention relates to the field of apoptosis, in particular, it relates to apoptosis-modifying fusion proteins with at least two domains, one of which targets the fusion proteins to a target cell, and another of which modifies an apoptotic response of the target cell. For example, fusing various cell-binding domains to Bcl-XL and Bad allows targeting to specific subsets of cells in vivo, permitting treatment and/or prevention of cell-death related consequences of various diseases and injuries. This technology could be used to minimize or prevent apoptotic damage that can be caused by neurodegenerative disorders, *e.g.,* Alzheimer's disease, Huntington's disease or spinal-muscular atrophy, stroke episodes or transient ischemic neuronal injury, *e.g.,* spinal cord injuries. Additionally, apoptotic-enhancing fusion proteins of the current invention could be used to inhibit cell growth, *e.g.,* uncontrolled cellular proliferation.

DNA Binding Protein and Sequence as Insulators Having Specific Enhancer Blocking Activity for Regulation of Gene Expression

Adam C. Bell, Adam G. West, Gary Felsenfeld (NIDDK)

DHHS Reference Nos. E–220–98/0 filed 30 Jun 1999 and E–220-98/1 filed 19 Apr 2000

Licensing Contact: Girish Barua; 301/496–7735 ext. 263; e-mail: gb18t@nih.gov

This patent application has two components. The first is the identification of a functional 50bp fragment of a previously known chicken chromatin insulator protein. The second component is the identification of the REBL (Required for Enhancer Blocking) CTCF protein (CCCTC-binding factor) which binds to the 50bp fragment. [The relationship between these two can be analogized as a receptor (50 bp fragment) and its ligand (the REBL CTCF protein).] These two elements can be used separately or together to regulate gene expression.

An insulator is a DNA sequence which is capable of acting as a barrier to neighboring cis-acting elements, preventing gene activation when juxtaposed between an enhancer and a promoter (*i.e.,* when the insulator is placed between the enhancer and the promoter gene activation is blocked). An insulator will also act to protect a stably integrated reporter gene from position effects. This 50 bp fragment represents a functionally active domain of the chicken insulator protein which is both necessary and sufficient for enhancer blocking activity in human cells. The previously described chicken chromatin insulator is a 1.2 kb fragment which, where overall size of the vector to be delivered is a concern, for example, in gene therapy, may be too large for some applications. The identification of this active 50 bp fragment may therefore be a preferred alternative.

The identification of the REBL CTCF protein as an agent which binds to the 50 bp insulator fragment and whose binding activity is necessary for blocking of enhancer activity provides an additional element which may be used to more specifically control gene regulation. As most gene expression is dependent on the activity of multiple components the identification of a specific binding factor which functions as a blocking enhancer activity may permit more precise control of gene expression. The human REBL protein has regions which share homology with previously disclosed partial human cDNAs. It has a molecular weight of 135 kDa. A chicken homolog has also been identified. CTCF was originally identified as a repressor of the chicken c-myc gene.

Dated: August 29, 2000.

Jack Spiegel,

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

[FR Doc. 00–22880 Filed 9–6–00; 8:45 am]

BILLING CODE 4140–01–U

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by contacting Marlene Shinn, J.D., at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7056 ext. 285; fax: 301/402–0220; e-mail: shinnm@od.nih.gov. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Inhibition of Smad3 To Prevent Fibrosis and Improve Wound Healing

Anita B. Roberts *et al.* (NCI)

DHHS Reference No. E–070–00/0 filed 19 May 2000; PCT/US00/13725

Millions of dollars are spent each year to heal chronic non-healing wounds and in the treatment of severe burn patients. The NIH announces a new technology that may lead to improved approaches to treatment of burn patients and the reduction of scarring and more rapid closure of both acute (surgical) and chronic wounds (e.g., diabetic, decubitus, and venus statis ulcers).

Smad2 and Smad3 are highly homologous cytoplasmic proteins which function to transduce signals from Transforming Growth Factor-beta (TGF–β) and activin receptors to promoters of target genes found in the nucleus. This new technology indicates that interference with specific signaling pathways downstream of TGF–β may be more selective and have a better outcome than approaches aimed at blocking all effects of this pleiotropic cytokine. Specifically, it is proposed that elimination or inhibition of Smad3 may interfere with fibrogenic mechanisms and reduce the accumulation of scar tissue associated with high dose radiation and wound healing, while increasing the rate of re-epithelialization of wounds.

Although this technology is still in an early stage, our researchers have obtained solid evidence of the involvement of Smad3 in these processes by use of a Smad3 null mouse model which they have developed. Based on these results, it is believed that antisense Smad3 or small molecule inhibitors of Smad3 will have clinical applications in wound healing, in improving growth and reducing unwanted fibrosis of autologous skin grafts for treatment of burn patients, and in treatment of radiation fibrosis and other fibrotic diseases associated with chronic inflammation. In addition, the discovery of inhibitors to Smad3 signaling may lead to radiation dose escalation and accelerated tumor cell death while reducing the side effects associated with radiation therapy.

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

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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]

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