The notch gene belongs to a family of epidermal growth factor (''EGF'') like homeotic genes, which encode transmembrane proteins with a variable number of cystgeine-rich EGF-like repeats in the extracellular region. Four notch genes have been described in mammals, which include notch-1, notch-2, notch-3, and notch-4 (Int-3), which have been implicated in the differentiation of the nervous system and other structures. The EGF-like proteins Delta and Serrate have been identified as ligands of notch-1.

Mature notch proteins are heterodimeric receptors derived from the cleavage of notch pre-proteins into an extracellular subunit (N^{EC}) containing multiple EGF-Like repeats and a transmembrane subunit including intracellular region (N^{tm}). Notch activation results from the binding of ligands expressed by neighboring cells, and signaling from activated notch involves a network of transcription regulators.

Alteration of notch-1 signaling or expression may contribute to tumorigenesis. Deletions of the extracellular portion of human notch-1 are associated with about 10% of the cases of T-Cell acute lymphoblastic leukemia. Truncated forms of notch-1 cause T-Cell lymphomas when introduced into mouse bone marrow stem cells and are onogenic in rat kidney cells. The human notch-1 gene is in a chromosomal region (9q34) associated with hematopoietic malignancies of lymphoid, myeloid, and erythroid lineage. Additionally, strikingly increased expression of notch-1 has been documented in a number of human tumors including cervical cancer, colon tumors, lung tumors, and pre-neoplastic lesions of the uterine cervix.

Notch antisense oligonucleotides (or other molecules that interfere with the expression or function of notch) could be therapeutically administered to treat or prevent tumors. It has not been found that administration of notch antisense oligonucleotide alone is ineffective as an anti-neoplastic treatment. The present invention has overcome this problem by combining the administration of a cell differentiation agent with a molecule that interferes with the expression or function of a notch protein (such as the notch-1 protein). This combination of approaches has unexpectedly been found to induce apoptosis in neoplastic cells, and provide a useful therapeutic application of this technology. The method of the present invention includes inducing apoptosis in a target cell by inhibiting a cell fate determining function of a notch protein in the target cell at a time when the cell is undergoing differentiation. In particular, the target cell is induced to differentiate and upregulate notch expression, so that interference with notch expression or function causes the target cell to commit to an apoptotic pathway. Inhibition of notch expression or interference with its function can include exposing the cell to a notch protein antisense oligonucleotide that includes at least six nucleotides that comprise a sequence complementary to at least a portion of the RNA transcript of a notch gene (such as the notch-1 gene), and is hybridizable to the RNA transcript. Although the antisense oligonucleotide can be hybridizable to any region of the RNA transcript, particular oligonucleotides that have been found to be useful are antisense oligonucleotides to the notch-1 EGF repeat region, Lin/notch region, or ankyrin region. Alternatively the molecule can be a monoclonal antibody that antagonizes the function of a notch protein in the cell.

In particular the tumor cell is one that is characterized by increased activity or increased expression of a notch protein, such as a notch-1 or notch-2 protein. Examples of tumor types that over express notch-1 include cervical cancer, breast cancer, colon cancer, melanoma, seminoma, lung cancer and hematopoietic malignancies, such as erythroid leukemia, myeloid leukemia, (such as chronic or acute myelogenous leukemia), neuroblastoma and medulloblastoma. The differentiation inducing agent to which the cell is exposed can be selected from a broad variety of agents, including retinoids, polar compounds (such as hexamethylene bisacetanmide), short chain fatty acids, organic acids, Vitamin D derivatives, cyclooxygenase inhibitors, arachidonate metabolism inhibitors, ceramides, diacylglycerol, cyclic nucleotide derivatives, hormones, hormone antagonists, biologic promoters of differentiation, and derivatives of any of these agents.

Technology

This invention provides a method and pharmaceutical composition for treating a tumor by causing apoptosis in tumor cells that expresses notch-1 protein, and in particular cells that exhibit increased expression of notch-1. Hence, this technology discloses methods and compositions to induce apoptosis in cells that over express the notch proteins. A cell fate determining function of notch is specifically disrupted at a time when the cell is undergoing differentiation, which causes the cell to undergo apoptosis. The invention includes therapies for tumors that over express a notch protein (such as notch-1) by inducing differentiation of the cells in the tumor with a differentiation inducing agent such as hexamethylene bisacetamide and other such differentiation agents. At a time during which differentiation has been promoted, and the cell is susceptible to interference with the anti-apoptosis effect of notch, the function of the notch protein is disrupted. Disruption of notch function can be achieved, for example, by the expression of antisense oligonucleotides that specifically interfere with expression of the notch protein on the cell, or by monoclonal antibodies that specifically bind to notch and inactivate it. This technology represents a novel method to induce apoptosis in tumor cells.

The above mentioned invention is available, including any available foreign intellectual property rights, for licensing.

Dated: August 3, 1999.

Jack Spiegel,

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

[FR Doc. 99–20455 Filed 8–6–99; 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.

Direct C–14 Oxidation of Opioids

A Coop and KC Rice (NIDDK)

Serial No. 60/132,628 filed 05 May 1999, Licensing Specialist: Leopold J. Luberecki, Jr.; 301/496–7735 ext. 223; e-mail: leo__luberecki@nih.gov.

This application describes a simple one-step method for the direct oxidation of 14-H opioids into the desired 14-hydroxy opioid derivatives, providing a quicker and less expensive means for the manufacture of these compounds. For example, this process converts codeinone into 14-hydroxycodeinone, eliminating the need for using thebaine, the currently used common starting material, whose price is increasing at 10% annually. The invention claims a process of employing certain oxidizing agents, using much less reagent volume than the present standard. The invention also circumvents diene intermediate formation, thus eliminating the need for expensive chromatographic isolation. The process takes much less time than the industry standard and produces high yields between 50% and 80% at higher cost-effectiveness than current methods. The 14-hydroxyl substituted opioid antagonists are useful in a number of medicinal applications. For instance, the antagonists naltrexone and naloxone are drugs used in the treatment of opiate abuse, opiate overdose, and alcohol addiction. In addition, certain derivatives of these compounds have been found useful in the prevention of tolerance to morphine and as immunosuppressants.

Methods for Detecting Cancer Cells

Thomas Ried, Evelin Schrock, Bijan M. Ghadimi (NHGRI)

DHHS Reference No. E–211–98/0 filed 01 Apr 1999, Licensing Contact: John Fahner-Vihtelic; 301/496–7735 ext. 270; e-mail: jf36z@nih.gov

The present application describes a highly sensitive assay for distinguishing between cancer and non-cancer epithelial cells in the blood. It provides an improved diagnostic technique for detecting cancer and determining the organ-origin of the cancer. This assay can be used to prove the neoplastic nature of cells and predict when shed tumor cells have or will become metastatic. A major advantage of the present invention is that tumor cells can also be recovered as viable cells. Thus, the tumor cells can be kept alive in vitro for a sufficient period of time to determine the effect of particular anti-tumor pharmaceuticals on the cells. Furthermore, the assay provides an early detector of treatment success or failure and thereby allows a treatment regimen to be customized for an individual patient with advanced primary cancer.

Replication-Defective Dengue Viruses that are Replication-Defective in Mosquitoes for Use as Vaccines

L Zeng, L Markoff (FDA)

Serial No. 60/098,981 filed 01 Sep 1998, Licensing Contact: Carol Salata; 301/496–7735 ext. 232; e-mail cs253n@nih.gov

Although flaviviruses cause a great deal of human suffering and economic loss, there is a shortage of effective vaccines. The present invention is directed toward vector stage replication-defective flaviviruses that are replication-defective in mosquito vectors that transmit them to humans. The replication-defective flaviviruses of the present invention demonstrate a limited ability to replicate in the vector organisms that transmit flaviviruses from one host to another. More specifically, the present invention is directed toward the construction and propagation of flaviviruses that possess 3'-noncoding regions altered in such a way as to prevent or severely limit viral reproduction in a vector organism. Such mutant flaviviruses may be useful as vaccines.

Vaccine Against Eschericha coli 0157 Infection, Composed of Detoxified LPS Conjugated to Proteins

Shousun C. Szu, Edward Konadu, and John B. Robbins (NICHD) DHHS Reference No. E–158–98/0 filed 20 July 1998 (PCT/US98/14976)

Licensing Contact: Robert Benson; 301/496–7056 ext. 267; e-mail: rb20m@nih.gov

This invention is a conjugate vaccine to prevent infection, in particular in young children under 5 years of age, by E. coli 0157:H7, an emerging human pathogen which causes a spectrum of illnesses with high morbidity and mortality, ranging from diarrhea to hemorrhagic colitis and hemolytic-uremic syndrome (HUS). Infection is due to the consumption of water or meat contaminated by feces from infected animals, such as cattle. The conjugate is composed of the O-specific polysaccharide isolated from E. coli 0157, or other Shiga-toxin producing bacteria, conjugated to carrier proteins, such as non-toxic P. aeruginosa exotoxin A or Shiga toxin 1. A Phase I clinical trial, involving adult humans, showed the vaccine is safe and highly immunogenic. Adults, after one injection containing 25 (g of antigen, responded with high titers of bactericidal antibodies. Thus the conjugates of the invention are promising vaccines, especially for children and the elderly, who are most likely to suffer serious consequences from infection. The clinical study is described in J. Infectious Diseases 177, 383–387, 1998.

Applicator System and Method of Use

Michael J. Lenardo, Galen Fisher (NIAID)

Serial No. 09/005,475 filed 12 Jan 1998, Licensing Contact: John Fahner-Vihtelic, 301/496–7735 ext. 270

The present application describes a novel microcentrifuge tube and tube cap and research method, which allows for dispensing the contents of a microcentrifuge tube without pipetting. The design eliminates pipetting volume error and prevents the cross-contamination which can be experienced in conventional pipetting. This invention is particularly useful for such applications as loading tube contents into an electrophoresis gel after a reaction such as PCR. Using the disclosed apparatus and methods increases the speed of a variety of routine procedures and prevents contamination of samples due to soiled lab apparatus.

Method To Reduce the Bias in the Mean and Variance of Indices of Water Diffusion Anisotropy as Measured by Diffusion Tensor MRI

Carlo Pierpaoli (NINDS/NICHD), Peter J. Basser (NICHD)

Serial No. 08/824,706 filed 14 Apr 1997; Licensing Contact: John Fahner-Vihtelic; 301/496–7735, ext. 270; e-mail: jf36z@nih.gov.

This invention describes several novel MRI ''stains'' to measure and display water diffusion anisotropy data obtained by diffusion tensor MRI (DT–MRI). One problem that this invention overcomes is that it significantly reduces the statistical bias in the mean and variance of the measured anisotropy of water diffusion caused by background noise in the MR images. These benefits are achieved by exploiting the idea that fiber tracts exhibiting diffusion anisotropy vary continuously in most regions. Thus, the principal axes of the diffusion tensor (or eigenvectors) can be used to improve the estimate of the principal diffusivities (or eigenvalues) within a local region of interest. These eigenvalues, in turn, are used to

compute our improved local measures of diffusion anisotropy. Images or maps of water diffusion anisotropy are increasingly being used to gather structural information about fibrous tissue, such as white matter fibers as well as cardiac and skeletal muscle fibers in vivo, in health, disease, development, and aging. This invention results not only in a more accurate measurement of diffusion anisotropy, but it improves image quality and reduces scanning time in clinical and biological applications of DT–MRI. Since the reduction in diffusion anisotropy has been shown to be sensitive to nerve fiber degeneration, this new data should be useful in studies to screen for and determine the efficacy of neuroprotective agents, as well as streamline multi-site and longitudinal clinical trials designed to assess their safety and efficacy.

A New Class of Anti-Tumor Agents

Christopher J. Michejda (NCI), Richard H. Smith, Jr.

Serial No. 07/179,622 filed 29 Mar 1988; U.S. Patent 4,9023,970 issued 08 May 1990; Licensing Contact: Girish Barua; 301/496–7056, ext. 263; e-mail: gb18t@nih.gov

Substituted triazenes are potentially useful anti-tumor agents. Examples of substituted triazenes in clinical use include 5-(dimethyltriazeno)imidazole-4-carboxamide (DTIC), which is used in the treatment of metastatic melanoma and some soft tissue sarcomas, and the recently approved temozolomide, which is used in brain cancer. The National Institutes of Health has developed compounds which have many advantages over known triazene anti-cancer compounds. Advantages include a novel mechanism of action for at least one of them, namely, 1-(2-chloroethyl)-3-(N-methylcarbamoyl)-methyltriazene, which is a highly selective, non-toxic anti-tumor compound, their well understood chemistry, and ease of synthesis of new analogs.

The technology covers compounds of the series of 1-(2-chloroethyl)-3-acyl-3-alkyltriazenes and a method for their synthesis. Some of the subject acyl triazenes generate 2-chloroethyldiazonium ions at very easily controlled rates, while others require metabolic activation to release the electrophilic agent.

Several of the acyltriazenes have shown excellent in vivo activity against human tumor xenografts in nude mice and low toxicity. These compounds are good candidates for development as anti-tumor drugs.

Dated: August 3, 1999.

Jack Spiegel,

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

[FR Doc. 99–20456 Filed 8–6–99; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

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ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by contacting Susan S. Rucker, J.D., Patent and Licensing Specialist, Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7057 ext. 245; fax: 301/402–0220; e-mail: sr156v@nih.gov. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Lentivirus Vector System

SK Arya (NCI)

Serial No. 60/115,247 filed 07 Jan 1999

This application relates to the field of gene therapy. More, particularly the application describes a vector system useful in gene therapy. The vectors employed in this system are lentiviral vectors, particularly retroviral vectors based on HIV2. Retroviral vectors based on HIV2, unlike most other retroviral vectors such as MuLV, are capable of infecting non-proliferating cells thereby making them useful in situations where other retroviral vectors are not. The vector system uses a two vector approach to minimize the possibility of HIV infection and comprises a transfer vector, for carrying the foreign gene of interest, and a packaging vector. The vector system demonstrates an improved ability to package the gene of interest when compared to a control without a loss in production of the transgene. In the experimental system this increase was 25 fold. This improved packaging ability is one means to address current low viral titers which are problematic in the gene therapy field.

This research has been published, in part, in Human Gene Therapy 1998 June 10; 9(9): 1371–86.

Thymosin β4 Promotes Wound Repair

KM Malinda, HD Kleinman (NIDCR) and A Goldstein

Serial No. 60/094,690 filed 30 Jul 1998

This application describes the use of the compound thymosin β4 as an agent for promoting wound healing. Thymosin β4 is a small, 43 mer, 4.9 kDa, peptide which can be produced by chemical synthesis or recombinantly. Studies using a punch model for wounds in rats have shown that providing thymosin β4 either by systemic delivery (intraperitoneal) or topical delivery accelerates wound healing and that extracellular matrix deposition occurs in the wound bed. In addition, thymosin β4 has been shown previously to promote endothelial cell migration and to promote angiogenesis.

Mammalian Selenoprotein Differentially Expressed in Tumor Cells

VN Gladyshev (NCI), DL Hatfield (NCI), JC Wooten (NLM) and K Jeang (NIAID)

PCT/US99/07560 filed 06 Apr 1999 and Serial No. 60/080,850 filed 06 Apr 1998

This application describes the identification, cloning, and sequencing of a human protein which contains selenium. A murine homolog has also been identified. The gene encoding the protein has been localized to the short arm of chromosome 1 at 1p31. Early work indicates that levels of the protein and/or mRNA are decreased in prostate, liver, ovarian and fallopian tube cancers and in lymphoma. Thus, levels of the protein or mRNA may be useful clinically as diagnostic or prognostic tools. The fact that other selenium proteins are known to be involved in the immunological response and the fact that this protein was originally detected in T cells leads to a hypothesis that the protein may play a role in the immunological response. Antibodies and tools for expressing the protein recombinantly may be useful in conducting further research on the functionality of this protein. This selenoprotein may potentially mediate a chemopreventative effect of selenium in prostate cancer.