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 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.

Novel Molecular Conjugates for Signal Amplification

Subhash Dhawan (CBER/FDA), DHHS Reference No. E–136–02/0 filed 10 Jun 2002, Licensing Contact: Susan Ano; 301/435–5515; *anos@od.nih.gov.*

This invention relates to novel molecular conjugates that are applicable to the field of immunoassays and, in general, any probe assay requiring detection of an analyte. These molecular constructs are capable of enhancing test sensitivity and shortening assay time through the use of analyte-specific binding reagents associated with a multiple label scaffold. The invention can utilize a diversity of analyte-binding molecules, providing adjustable selectivity for a range of analytes. Conversely, combination of labels with different chemical properties with a single binding partner facilitates a multiplex approach to analyte detection on a large scale. The invention includes kits and methods for production and use of the molecular conjugates.

Methods of Inducing Deacetylase Inhibitors To Promote Cell Differentiation and Regeneration

Vittorrio Sartorelli (NIAMS) and Pier L. Puri, DHHS Reference No. E–353–01/0 filed 18 Oct 2001, Licensing Contact: Fatima Sayyid; 301/435–4521; *sayyidf@od.nih.gov.*

The present invention discloses a method of enhancing progenitor cell differentiation, including enhancing myogenesis, neurogenesis and hematopoiesis, by contacting a progenitor cell with an effective amount of a deacetylase inhibitor (DI). The progenitor cell can be part of cell culture, such as a cell culture used for in vitro or in vivo analysis of progenitor cell differentiation, or can be part of an organism, such as a human or other mammal. Contacting the progenitor cell with a DI can lead to enhancement of expression of terminal cell-type specific genes in the progenitor cell, such as enhancing expression of muscle-specific genes in myoblasts, and can lead to skeletal muscle hypertrophy. Administering a DI to a subject also can provide some prophylactic or therapeutic effect for inhibiting, preventing, or treating associated with a degeneration or loss of tissue. The DI can be administered to a subject as part of a pharmaceutical composition.

FcεRI-Bearing Human Mast Cell Lines

Arnold Kirshenbaum, Cem Akin, Dean D. Metcalfe (NIAID), DHHS Reference No. E–279–01/0 filed 04 Feb 2002, Licensing Contact: Marlene Shinn; 301/435–4426; *shinnm@od.nih.gov.*

Allergic diseases, which include asthma, are a significant health problem in the United States, with 15–25% of the population displaying some form of allergies. The mast cell is the major effector cell of allergic inflammation and has also been shown to be involved in delayed hypersensitivity reactions, fibrosis, autoimmune disorders, neoplasia, and immunity against parasitic infections. Most mast cell studies are currently performed using mast cells derived from cultured CD34+ progenitor cells, which is time consuming, costly, and produces a poor yield of cells.

The NIH announces a number of newly derived mast cell lines that more closely resemble normal in vivo and in vitro human mast cells, which express functional FcεRI receptors and respond to Stem Cell Factor (SCF) with proliferation. It is well known that the most important means by which mast cells induce inflammation is by mediator release via FcεRI receptor cross-linking. These cell lines also release mediators by cross-linking of FcγRI (CD64) receptors, and have been shown to express FcγRII (CD32). It is anticipated that these cell lines will be useful in a variety of research projects including the development of drugs that block the release of potent mediators that cause allergic inflammation and the development of drugs to inhibit mast cell hyperplasia and dysmyelopoiesis in mastocytosis.

Thermolabile Hydroxyl Protecting Groups and Methods of Use

Serge L. Beaucage et al. (FDA), DHHS Reference No. E–242–00/0 filed 03 Dec 2001, Licensing Contact: Marlene Shinn; 301/435–4426; *shinnm@od.nih.gov.*

Synthetic oligonucleotides can be used in a wide variety of settings, which aside from basic research tools include gene therapy applications, antisense and immunostimulatory therapeutic indications, and the rapidly evolving diagnostic and DNA sequencing microarray technology. The NIH announces a new technology aimed at improving oligonucleotide synthesis on glass microarrays. The technology is based on the use of thermolabile groups for 5′-/3′-hydroxyl protection of oligonucleotides and departs from the current methods employed in the preparation of oligonucleotide microarrays in that it does not utilize photochemical irradiation or abrasive chemicals for the removal of such protecting groups. Instead, thermal cleavage of 5′-/3′-hydroxyl protecting groups is effected at temperatures near 90°C under mild neutral conditions to prevent glass surfaces from being harmed by harsh chemical reagents. In addition, thermolabile protecting groups could be useful in manufacturing synthetic oligonucleotides on solid supports or in solution. Thermolabile protecting groups may also be used to protect/deprotect drug functional groups under conditions that will not affect other functional entity(ies) on the molecule.

Dated: October 24, 2002.

Jack Spiegel,

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

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Identification of a Novel BHD Gene

Laura S. Schmidt (NCI), DHHS Reference Nos. E–190–02/0 filed 31 May 2002 and E–190–02/1 filed 20 Jun 2002, Licensing Contact: George Pipia; 301/435–5560; *pipiag@od.nih.gov.*

Birt-Hogg-Dube (BHD) syndrome is an inherited autosomal dominant neoplasia syndrome characterized by benign hair follicle tumors and is associated with a higher risk for developing renal cancer, spontaneous pneumothorax and /or lung cysts.

The present invention describes identification of the BHD syndrome associated germline mutations in a novel human gene, herein called BHD gene. This gene encodes for the protein, folliculin, functions of which remain currently unknown.

This discovery makes possible the development of a diagnostic method for BHD syndrome using a simple blood test. The test is particularly useful in detecting BHD mutations in asymptomatic carriers within BHD families.

Patients with kidney tumors can be evaluated for BHD gene mutations using a similar genetic diagnostic test, which will allow for a more accurate diagnosis of a kidney cancer and improved patient prognosis. The BHD encoding sequence is the third gene found to be responsible for inherited kidney cancer, and mutation testing allows for a correct diagnosis and initiation of the proper treatment, which is different for each of the types of kidney cancer caused by the three genes.

Methods of using BHD encoding sequence also allows for a differential genetic diagnosis of spontaneous pneumothorax, or collapsed lung. Since collapsed lung can be caused by several factors, a BHD diagnostic test allows a physician to determine predisposition and recurrence of additional spontaneous pneumothoraces due to mutation(s) in the BHD gene.

The discovery should also lead to the development of novel pharmaceutical products and methods for treating BHD skin lesions using creams containing the BHD gene product, folliculin. Such products and methods of treatment are expected to reduce the size and appearance of the benign hair follicle tumors.

The disclosed technology will provide new and exciting methodologies to correctly diagnose BHD syndrome and should lead to the development of novel pharmaceutical reagents for treatment of BHD skin lesions as well as other skin diseases.

Novel Anti-CD30 Antibodies and Recombinant Immunotoxins Containing Disulfide-Stabilized Fv Fragments

Ira H. Pastan et al. (NCI), DHHS Reference No. E–135–02/0 filed 07 Jun 2002, Licensing Contact: Jonathan Dixon; 301/435–5559; *dixonj@od.nih.gov.*

The present invention discloses the creation of new anti-CD30 stalk antibodies and anti-CD30 dsFv-immunotoxins, which have shown good cytotoxic activity.

CD30 is a member of the tumor necrosis factor receptor super family. It is an excellent target due to its high expression in malignant Reed Sternberg cells of Hodgkin's Lymphoma (HL) and in anaplastic large cell lymphomas (ALCL), and due to its expression in only a small subset of normal lymphocytes. Previous attempts to target CD30 include the scFv immunotoxin Ki-4 that has shown specific binding to CD30-positive lymphoma cell lines and killed target cells.

The immunotoxins of the present invention are more stable and have higher affinity for CD30 then their predecessors. Research thus far has shown that the dsFv-immunotoxins are able to kill a variety of CD30-positive lymphoma cell lines in vitro as well as CD30-transfected A431 cells via specific binding to CD30.

As claimed in this patent application, the antibodies are able to bind to the stalk or to a cleavage site that is destroyed when sCD30 is cleaved away. This enhancement further increases the ability of immunotoxins to target and treat lymphomas expressing CD30.

The researchers are also interested in seeking a partner(s) under a Cooperative Research and Development Agreement (CRADA). For information on this CRADA opportunity, please contact Dr. Patrick Twomey of the NCI Technology Transfer Branch at twomeyp@mail.nih.gov.

Cytotoxic Agents Delivered Into Tumor Cells Through Specific Cell Surface Receptors and Conjugates of Ligand, Linker and Cytotoxic Agent and Related Compositions and Methods of Use

DHHS Reference No. E–057–02/0 filed 27 Feb 2002 and DHHS Reference No. E–057–02/1 filed 05 Apr 2002, Nadya Tarasova, Christophe A. Michejda, Marcin Dyba, Carolyn Cohran (NCI), Licensing Contact: George Pipia; 301/435–5560; *pipiag@od.nih.gov.*

Systemic toxicity of drugs is one of the most serious problems in cancer chemotherapy and frequently is dose limiting. Specific delivery of cytotoxic drugs to cancer cells remains among the most intractable problems of cancer therapy. Targeted delivery of anti-proliferation drugs through the cell surface receptors that are over expressed on cancer cells can reduce systemic toxicity and increase effectiveness of a treatment.

The present invention describes cytotoxic compounds with an intracellular target that can selectively enter tumor cells through specific receptors on the cell surface. The invention also describes a conjugate comprising a cytotoxic agent, a linker arm and a ligand capable of delivering a cytotoxic agent in a cell specific manner. Such conjugates of a cytotoxic agent and a ligand (delivery moiety) have increased selectivity for tumor cells. The toxic moiety and the ligand are joined by a linker arm that is stable in circulation, but is easily cleaved in lysosomes upon internalization of the conjugate. A panel of compounds comprised of a variety of cytotoxic warheads, against various intracellular targets linked to an assortment of ligands, has been developed and tested in a model system. Ligand moieties of these conjugates are capable of specific delivery of cytotoxic agents to receptors that are frequently over expressed in gastric, colon, lung, breast, ovarian and pancreatic tumors. These compounds have the potential to be highly effective anti-tumor agents with considerably little negative effect. This disclosed technology could provide new and exciting methodologies to treat cancer.

Novel Form of MRP9 in Breast Cancer

I. Pastan, T. Bera, and B. Lee (NCI), U.S. Provisional Patent Application 60/350,053 filed 17 Jan 2002, Licensing Contact: Brenda Hefti; 301/435–4632; *heftib@od.nih.gov.*

MRP9 is a member of the ATP binding cassette (ABC) transporter super family. This gene has at least two splice variants, one of which is membrane-associated and expressed in normal breast, breast cancer and testis, and the other of which is expressed in several other tissues. Anti-peptide antibodies designed to react with the amino terminus of the protein detect only the variant found in breast and testis. This protein should be a useful target for immunotherapy in breast cancer.

The patent application has claims directed towards use of MRP9 in detecting various cancers, including breast, testicular and pancreatic cancers. The application also contains claims directed toward immunotherapeutic agents, which could be useful to treat said cancers.

Use of a Histone Deacetylase Inhibitor To Increase the Entry of an Adenoviral Agent into a Cell

Tito A. Fojo *et al.* (NCI), DHHS Reference No. E–198–01/0 filed 24 Aug 2001, Licensing Contact: Matthew Kiser; 301/435–5236; *kiserm@od.nih.gov.*

This technology is directed to the use of any histone deacetylase inhibitor, including but not limited to FR901228 (depsipeptide, FK228), to increase the expression of Coxsackie-Adenovirus Receptor (CAR) and/or ''-'' integrins on the surface of a cell, such as a normal or cancerous cell, so as to increase the entry into the cell of a subsequently administered adenovirus-based therapeutic agent.

This disclosed method comprises exposing a cell to a histone deacetylase inhibitor in an amount sufficient to increase the expression of CAR and/or ''-'' integrin on the surface of the cell and, simultaneously with or subsequently to, exposing the cell to an adenoviral agent, whereupon the uptake of the adenoviral agent by the cell is increased relative to an otherwise identical cell that has not been exposed to a histone deacetylase inhibitor.

PEGylation of Linkers Improves Antitumor Activity and Reduces Toxicity of Immunoconjugates

I. Pastan, Y. Tsutsumi, M. Onda, S. Nagata and B. Lee (NCI), DHHS Reference No. E–216–00/2 filed 08 Jun 2001 (PCT Application PCT/US01/18503), Licensing Contact: Jonathan Dixon; 301/435–5559; *dixonj@od.nih.gov.*

The present invention relates to site-directed PEGylation of immunoconjugates. In particular, it provides a new approach for modifying with polyethylene glycol (PEG) a connector molecule that attaches the toxin moiety to the targeting moiety of an immunotoxin. The PEGylated immunotoxin has comparable *in vitro* specific toxicity against tumor cells, but other properties including stability, plasma half-life, antitumor activity, immunogenicity and non-specific toxicity are greatly improved.

The application contains composition of matter claims towards PEGylated connector molecules and method claims for using said PEGylated connector molecules.

Inhibitor of DNA Methylation

Victor E. Marquez (NCI), Erik Selker, Cindy Matson, Sheldon Greer, Peter Jones, PCT filing claiming priority to 60/309,242 filed on July 31, 2001, Licensing Contact: Brenda Hefti; 301/435–4632; *heftib@od.nih.gov.*

DNA methyltransferases (also referred to as DNA methylases) transfer methyl groups from the universal methyl donor S-adenosyl methionine to specific sites on a DNA molecule. When gene sequences contain many methylated cytosines, they are less likely to be expressed. Several such 'silenced' genes are now known to be an important contributing factor in many cancers where expression of tumor suppressor genes has been suppressed. Preventing DNA methyltransferase production, or inhibiting the enzyme, may allow tumor suppressor genes that have been silenced by hypermethylation to be re-activated. Re-activation of tumor suppressor genes is intended to stop or slow tumor growth by restoring growth control mechanisms. Thus, there exists a need for an effective, stable, and low-toxicity inhibitor of DNA methylation.

The inventors have discovered a potent inhibitor of DNA methylation that can specifically reactivate silenced tumor suppressor genes. This agent can be used to inhibit methylation and thereby combat certain cancers that have been linked to hypermethylation. This agent has also been shown in initial animal testing to be active orally and is more stable than some other agents in this same area of therapy and is a suitable candidate for further pre-clinical and clinical development as an anti-cancer agent to be used as monotherapy and/or as an adjunct to existing anti-cancer therapeutics.

Dated: October 24, 2002.

Jack Spiegel,

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Public Health Service and National Institute of Environmental Health Sciences; Notice of a Meeting of the Scientific Advisory Committee on Alternative Toxicological Methods

December 5, 2002.

Pursuant to section 10(a) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2), notice is hereby given of a meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) beginning at 9 AM on December 5, 2002, in Salon C at the Crystal Gateway Marriott, 1700 Jefferson Davis Highway, Arlington, Virginia.

Background

The SACATM was chartered January 9, 2002, to fulfill section 3(d) of Public Law 106–545, the ICCVAM Authorization Act of 2000 [42 U.S.C. 285*l*–3(d)] and is composed of scientists from the public and private sectors (**Federal Register:** March 13, 2002: Vol. 67, No. 49, page 11358). The SACATM provides advice to the Director of the National Institute of Environmental Health Sciences (NIEHS), the Interagency Coordinating Committee on the Validation of Alternative Toxicological Methods (ICCVAM), and the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) regarding statutorily mandated duties of the ICCVAM and activities of the NICEATM. The committee's charter is posted on the Web at *http://iccvam.niehs.nih.gov* and is available in hard copy upon request from the NTP Executive Secretary (NTP Liaison and Scientific Review Office, NIEHS, PO Box 12233, Research Triangle Park, NC 27709; telephone: 919–541–0530; facsimile: 919–541–0295 or *wolfe.niehs.nih.gov*).

Agenda

The meeting is being held on December 5, 2002, from 9 AM until adjournment and is open to the public with attendance limited only by the space available. Although not required, pre-registration is preferred to assist in planning for adequate space. To pre-register for this meeting, please contact the NTP Executive Secretary (contact information above). Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable