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

Amino-Terminus-Modified Eosinophil-Derived Neurotoxin and Its Selective Toxicity to Kaposi's Sarcoma Cell Line, KS Y–1

Dr. Susanna M. Rybak and Dr. Dianne L. Newton (NCI)
Serial No. 60/106,732 filed 02 Nov 98
Licensing Contact: J.R. Dixon; 301/496–7056 ext. 206; e-mail: jd212g@nih.gov

The invention described in this patent application is related to the field of cancer/HIV therapeutics. More particularly, the invention relates to the creation and identification of a compound which, in *in vitro* assays, is selectively cytotoxic for Kaposi's sarcoma cells and therefore may prove useful for developing a therapeutic treatment for Kaposi's sarcoma. The compound, a derivative of human eosinophil-derived neurotoxin (''EDN''), was obtained by altering the mature EDN protein at its amino terminus. EDN, a ribonuclease, has previously been shown to be cytotoxic when delivered to cells as an immunotoxin. The EDN derivative of this patent application has been constructed by adding to the NH_2 terminus of the mature EDN protein the four (4) naturally-occurring COOH terminal amino acids of the signal sequence of EDN, SLHV. Normall, this signal sequence is cleaved from EDN to obtain the mature, functional protein.

Tissue Microarray For Rapid Molecular Profiling

O Kallioniemi, G. Sauter (NHGRI)
DHHS Reference No. E–007–99/0 filed 28 Oct 98
Licensing Contact: Richard Rodriguez; 301/496–7056 ext. 287; e-mail: rr154z@nih.gov

Recent advances in molecular medicine have provided new opportunities to understand cellular and molecular mechanisms of disease and to select appropriate treatment regimens with the greatest likelihood of success. The clinical application of novel molecular, genetic and genomic discoveries has been impeded by the slow and tedious process of evaluating biomarkets in large numbers of clinical specimens. The present invention provides a method of high-throughput molecular profiling of very large numbers of tissue specimens, such as tumors, with minimal tissue requirements. This procedure provides a target for rapid parrallel analysis of biological and molecular characteristics (such as gene dosage and expression) from hundreds of morphologically controlled tumor specimens. Multiple sections can be obtained from such tissue microarrays (''tissue chips'') so that each section contains hundreds or thousands of different tissue specimens that maintain their assigned locations. Different in situ analyses, such as histological, immunological, or molecular, are performed on each section to determine the frequency and significance of multiple molecular markers in a given set of tissues. This method can also be combined with other technologies such as high-throughput genomics surveys using NA microarrays. DNA microarrays enable analysis of thousands of genes from one tissue specimen in a single experiment, whereas the tissue microarrays make it possible to analyze hundreds or thousands of tissue specimens in a single experiment using a single gene or protein probe. Together the DNA and tissue microarray technologies will be very powerful for the rapid analysis of markers associated with disease prognosis or therapy outcome.

Inhibitors of Formation of Protease Resistant Prion Protein

B Chesebro, B Caughey, J Chabry, S Priola (NIAID)
Serial No. 09/128,450, filed 03 Aug 98
Licensing Contact: George Keller; 301/496–7735 ext. 246; e-mail: gk40j@nih.gov.

The current invention provides peptides and pharmaceutical compositions that are useful to inhibit formation of protease resistant prion proteins (PrPres) such as the PrPres associated with transmissible spongiform encephalopathies (TSE). Certain synthetic peptides which incorporate the most amyloidogenic region of the PrP protein can inhibit the formation of PrPres under conditions where it would otherwise be formed. Such specific inhibition of the formation of PrPres may prevent or slow the deposition of amyloid deposits in the tissues of animals that have been exposed to a TSE or are suffering from a neurodegenerative disorder having the characteristics of a spongiform encephalopathy. For more information, see Chabry, Jr. et al. (1998) Specific Inhibition of *in vitro* Formation of Protease-Resistent Prion Protein by Specific Peptides, *J. Biol. Chem. 273*, 13203–13207.

Transcriptional Activation of the C-Mos Oncogene Is Associated With Disease Progression in HIV Infection

DI Cohen (NCI)
Serial No. 60/093,121 filed 15 Jul 98
Licensing Contact: George Keller; 301/496–7735 ext. 246; e-mail: gk40j@nih.gov

the current invention provides methods of diagnosing and staging pathogenic lentivirus infections, specifically HIV, by detecting activation of the *c-mos* gene. The binding of the HIV envelope glycoprotein, during cell-cell infection, to CXC chemokine receptors, leads to transcriptional activation of the c-mos gene. The invention also provides a method for treating a cell proliferative disorder associated with c-mos activity, such as HIV inspection, by treating a subject having the disorder with a composition that regulates *c-mos* activity or expression. In addition, compounds that modify *c-mos* express in specific cells can be identified, using this invention.

The HIV co-culture system can be used to initiate *c-mos* dependent cell death. Death in this system is dependent on the level of *c-mos* induction. Pharmacological agents that either also induce *c-mos*, or stabilize *c-mos* following its induction, would accelerate this death process. Therefore, this technology defines a method of screen for novel anti-proliferative drugs capable of interacting with this unique *c-mos* death pathway.

β_2-Microglobulin Fusion Proteins and High Affinity Variants

RK Ribaudo, M Shields (NCI)
Serial No. 60/088,813 filed 10 Jun 98

Licensing Conact: Peter Soukas; 301/496–7056 ext. 268; e-mail: ps193c@nih.gov

This invention concerns fusion proteins comprising (β_2M), a component of the MHC–1 complex, and immunologically active proteins such as the co-stimulatory molecule B7. The fusion proteins, and nucleic acids encoding them, have broad utility activating Cytotoxic T Lymphocytes (CTLs) against viruses and tumors. The fusion proteins locate to the surface of MHC–1 expressing cells. They may be used as adjuvants to enhance the efficacy of MHC–1 binding peptides, from viruses or cancer antigens, as vaccines. The fusion proteins can be used, *in vivo* or *ex vivo*, to enhance the immunogenicity of cancer cells to cause their destruction by the immune system. B7-β_2M is as effective at co-stimulating T-cells in comparison to anti-CD28 monoclonal antibodies, whereas wild-type β_2M is ineffective at co-stimulating T-cells. In addition, B7-β_2M induces better recognition and killing of tumor cell lines compared to wild-type β_2M. Another aspect of the invention is a mutant human β_2M that binds MHC–1 with higher affinity than wild-type β_2M. It can be used in place of wild-type β_2M, including in the fusion proteins, to greater effect.

Disubstituted Lavendustin a Analogs and Pharmaceutical Compositions Comprising the Analogs

VL Narayanan, EA Sausville, G Kaur, R Varma (NCI)
Serial No. 60/076,330 filed 27 Feb 98
Licensing Contact: Girish Barua; 301/496–7056 ext. 263; e-mail: gb18t@nih.gov

The invention discloses lavendustin A analogs that are protein tyrosine kinase (PTK) inhibitors having antiproliferative activity. A preferred compound, based on in vivo biological activity, is 4'-adamantylmethylbenzoate-1'-N-1,4-dihydroxybenzylamine. Pharmaceutical compositions comprising effective amounts of lavendustin are also covered; such compositions also may comprise other active ingredients and other materials typically used in such pharmaceutical formulations.

These compounds and compositions of the invention may be used for treating subjects to, for example, inhibit the proliferation of living cells for treatment of proliferative diseases.

Oligodeoxyribonucleotides Comprising O^6-Benzylguanine and Their Use

R Moschel et al. (NCI)
Serial No. 09/023,726 filed 13 Feb 98
Licensing Contact: Girish Barua; 301/496–7056 ext. 263; e-mail: gb18t@nih.gov

The invention provides single-stranded oligodeoxyribonucleotides which are more potent than O6-benzylguanine in inactivating human O^6-alkylguanine-DNA alkyltransferase (AGT). The oligodeoxyribonucleotides comprise from about 5 to 11 bases, at least one of which is a substituted or an unsubstituted O^6-benzylguanine. The oligodeoxyribonucleotides have several advantages over O^6-benzylguanine. They can inactivate mutant human AGTs that are either not inactivated or incompletely inactivated by O^6-benzylguanine. They have greater solubility in water than O^6-benzylguanine, and they react much more rapidly with AGT than does O^6-benzylguanine. The invention also provides compositions comprising such oligodeoxyribonucleotides. In addition, the invention provides a method of enhancing the effect of antineoplastic alkylating agents that alkylate the O^6 position of guanine residues in DNA for the chemotherapeutic treatment of cancer in a mammal.

Shielded Ultrasound Probe

H Wen, E Bennett (NHLBI)
DHHS Reference No. E–017–98/0 filed 12 Nov 97
Licensing Contact: John Fahner-Vihtelic; 301/496–7735 ext. 270; *e-mail*: jf36z@nih.gov

The invention relates to the recently developed imaging method called Hall Effect Imaging (HEI). HEI involves the use of a magnetic field and electrical or ultrasound pulses applied to an object to generate an image of the object. HEI has the potential to become a novel medical imaging technique, revealing features not seen in existing imaging methods. Performing HEI with conventional ultrasound transducers is difficult due to electrical interference, though. The present invention is a design for an ultrasonic transducer which overcomes these difficulties. This design may be made as a modification of a commercial ultrasound probe, thereby lowering the cost of development and production.

Methods for Use of Interleukin-4 (IL–4) and Tumor Necrosis Factor-Alpha (TNF–α) To Treat Human Immunodeficiency Virus (HIV) Infection

George N. Pavlakis, Antonio Valentin, Barbara K. Felber (NCI)
DHHS Reference No. E–160–96/1 filed 18 Sep 98 (claiming priority of U.S. Provisional 60/059,359 filed 19 September 1997)
Licensing Contact: J. Peter Kim, 301/496–7056 ext. 264; *e-mail*: jk141n@nih.gov

AIDS (acquired immunodeficiency syndrome), first reported in the United States in 1981, has become a worldwide epidemic, crossing all geographic and demographic boundaries. More than 475,000 cases of AIDS have been reported in the United States since 1981 and more than 295,000 deaths have resulted in the U.S. from AIDS. Over 1.5 million Americans are thought to be infected with HIV (human immunodeficiency virus), the causative agent of AIDS.

The subject invention relates to the interactions of the cytokines, interleukin-4 (IL–4) and tumor necrosis factor alpha (TNF-α), with HIV and HIV targets in the body. The invention provides methods for characterizing isolates of HIV according to susceptibility to the viral replication inhibiting effects of IL–4 and methods for use of TNF-α, IL–4, IL–4 analogs, and/or inhibitors of IL–4 to treat patients infected with specific isolates of HIV. The methods include a method for determining the prognosis of a patient infected with HIV, a method for down-regulating CCR5 expression in a cell, and methods for treating patients infected with CCR5 dependent isolate of HIV or CXCR4 dependent isolate of HIV.

Novel FUSE-Binding Protein and cDNA

DL Levens, RC Duncan, MI Avigan (NCI)
U.S. Patent 5,580,760 issued 03 Dec 96; U.S. Patent 5,734,016 issued 31 Mar 98; PCT/US97/21679 filed 21 Nov 97
Licensing Contact: Richard Rodriguez; 301/496–7056 ext. 287; *e-mail:* rr154z@nih.gov

This invention includes the gene sequence for a novel proto-oncogene binding protein that is valuable for studying the regulation of genes responsible for transforming normal cells to cancer cells. The c-myc proto-oncogene plays a central role in normal cell proliferation and programmed cell death; factors that inhibit its expression thus contribute to the formation of a variety of tumors. This newly isolated gene sequence encodes a protein that binds to the far-upstream element (FUSE) of the c-myc gene, which has been shown to be required to its maximal transcription. The FUSE-binding protein gene sequence may be used to analyze mutations, translocations, and other genetic derangements that are associated with abnormalities of the FUSE protein or c-myc expression. Such DNA probes also may be useful for diagnosing a variety of physiologic and pathologic

conditions, such as the transformation of normal cells to tumor cells. The FUSE-binding protein also may be used for developing mAbs that can be used to detect and quantitate the protein in biologic samples.

Fluorescent Hybridization Probes not Requiring Separation of Products

ME Hawkins, W Pfleiderer, MD Davis, FM Balis (NCI)
U.S. Patent 5,525,711 issued 11 Jun 96; U.S. Patent 5,612,468 issued 18 Mar 97; DHHS Reference No. E–155–96/1; PCT/US97/22448 filed 10 Dec 97
Licensing Contact: L. Manja R. Blazer; 301/496–7056 ext. 224; e-mail: mb379c@nih.gov

Fluorescent guanosine analogs (excitation at 340 nm, emission at 450 nm) are incorporated into oligonucleotides through a native deoxyribose linkage using automated DNA synthesis which allows them to base stack with native bases. As a result, slight changes in DNA structure can cause significant changes in spectral properties. These compounds are highly fluorescent as monomers in solution, but lose intensity in oligonucleotides. The use of these fluorophores as hairpin hybridization probes is based on the dramatic fluorescence increase that occurs upon them being squeezed out of the strand during annealing where the probe has not been provided with a base-pairing partner in the complementary strand. The degree of increase depends on the oligonucleotide sequence and the annealing strands' concentration. It allows the detection of specific DNA sequences in a mixture without separation of annealed and labeled products. These stable probes are treated as normal phosphoramidites during the DNA synthesis and subsequent de-blocking procedures.

This research has been published in Nucleic Acids Research, 23 (1995) 2872–2880 and Analytical Biochemistry, 244 (1997) 86–95.

Dated: January 13, 1999.

Jack Spiegel,

Director, Division of Technology Development and Transfer, Office of Technology Transfer.

[FR Doc. 99–1424 Filed 1–21–99; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; 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 section 552b(c)(4) and 552b(c)(6), Title 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 Cancer Institute Special Emphasis Panel, Shared Resources for Scientists Outside NCI Cancer Centers.

Date: February 17, 1999.

Time: 8:00 am to 6:00 pm.

Agenda: To review and evaluate grant applications.

Place: Ramada Inn Rockville, 1775 Rockville Pike, Rockville, MD 20852.

Contact Person: Sherwood Githens, PhD, Scientific Review Administrator, National Institutes of Health, National Cancer Institute, Special Review, Referral and Resources Branch, Executive Plaza North, 6130 Executive Boulevard, Bethesda, MD 20892, 301/435–9050.

(Catalogue of Federal Domestic Assistance Program Nos. 93.392, Cancer Construction; 93.393, Cancer Cause and Prevention Research 93.394, Cancer Detection and Diagnosis Research; 93.395, Cancer Treatment Research 93.396, Cancer Biology Research; 93.397, Cancer Centers Support; 93.398, Cancer Research Manpower; 93.399, Cancer Control, National Institutes of Health, HHS)

Dated: January 14, 1999.

LaVerne Y. Stringfield,

Committee Management Officer, NIH.

[FR Doc. 99–1427 Filed 1–21–99; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Allergy and Infectious Diseases; 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 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: Acquired Immunodeficiency Syndrome Research Review Committee.

Date: February 18–19, 1999.

Open: February 18, 1999, 8:00 am to 9:00 am.

Agenda: The meeting will be open for discussion of administrative details relating to committee business and program review, and for a report from the Director, Division of Extramural Activities, which will include a discussion of budgetary matters.

Place: Wyndham Washington Hotel, 1400 M Street NW, Washington, DC 20005–2750.

Closed: February 18, 1999, 9:00 am to adjournment on February 19, 1999.

Agenda: To review and evaluate grant applications.

Place: Wyndham Washington Hotel, 1400 M Street NW, Washington, DC 20005–2750.

Contact Person: Paula S. Strickland, PhD., Scientific Review Administrator, Scientific Review Program, Division of Extramural Activities, NIAID, NIH, Solar Building, Room 4C02, 6003 Executive Boulevard MSC 7610, Bethesda, MD 20892–7610, 301–402–0643.

(Catalogue of Federal Domestic Assistance Program Nos. 93.855, Allergy, Immunology, and Transplantation Research; 93.856, Microbiology and Infectious Diseases Research, National Institutes of Health, HHS)

Dated: January 14, 1999.

LaVerne Y. Stringfield,

Committee Management Officer, NIH.

[FR Doc 99–1425 Filed 1–21–99; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute on Drug Abuse; 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 a meeting of the National Advisory Council on Drug Abuse.

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