Adenovirus Mediated Transfer of Genes to the Gastrointestinal Tract

Crystal, R.G. (NHLBI)
Filed 16 Oct 91
Serial No. 07/776,057
Licensing Contact: Larry Tiffany, 301/496–7056 ext 206

A novel method of producing a chosen protein in the gastrointestinal tract of a human has been invented by and is available for licensing from the Public Health Service. The technology allows for the systemic long-term administration of a therapeutic protein to a patient without the need for periodic injections or suppositories. In comparison to alternative delivery systems, such as retroviral vectors, this methodology allows the gene of interest to be directly transferred to targeted cells even if these cells are not actively dividing. The technology is the subject of a pending patent application. (portfolio: Gene-Based Therapies—Therapeutics, vectors, viral; Gene-Based Therapies—Therapeutics, therapeutic genes)

Cytosine Deaminase Negative Selection System for Gene Transfer Techniques and Therapies

Mullen, C.A., Blaese, R.M. (NCI)
Serial No. 07/725,076
U.S. Patent No. 5,358,866 issued 25 Nov 94
Licensing Contact: Larry Tiffany, 301/496–7056 ext 206

A DNA construct has been developed which permits efficient expression of a modified bacterial cytosine deaminase (CD) gene in mammalian cells. The presence and expression of the gene has no apparent deleterious effects upon the transfected cells unless they are exposed to 5-fluorocytosine (5FC). Because CD has the ability to convert 5FC to a toxic antimetabolite, 5-fluorouracil, cells which have been transformed with the DNA construct can be selectively killed by treating them with 5FC. By modifying the specifity or method of delivering the DNA construct to cells, or by modifying the vector carrying the DNA construct to correspond to a tissue-specific promoter, specific cell or tissue types may be selectively eliminated from a subject.

Potential uses of the CD negative selective system (CDNSS) include gene therapy, immunotherapy, and bone marrow transplant applications.

The CDNSS could be used to regulate the biological activity of a transformed cell type as a part of a gene therapy application. For example, the CDNSS might be incorporated within a transformed cell type which also expresses a gene of therapeutic interest. The transformed cell type could then be administered to a subject. The biological activity expressed by the transformed cell type might be regulated by administering a measured dose of 5FC to the subject such that a portion of the transformed cell type is eliminated. Alternately, the transformed cell type might be eliminated from the subject by administering to the subject a dose of 5FC that would be toxic to the transformed cell type.

The CDNSS could also be used to impart immunity against a virus or a specific cell type, including a bacterium, a protozoan, or a type of tumor cell. For example, a cell type or virus harboring the CDNSS might be introduced into a subject to elicit an immune response against that cell type or virus. The introduced cell type or cells harboring the virus might be selectively killed after an immune response was elicited by administering 5FC to the subject.

The CDNSS could be used in conjunction with bone marrow transplant procedures to eliminate a specific cell type or virus from the bone marrow. For example, bone marrow cells from a subject might be transduced with a vector which harbors the CDNSS and which is specific for a certain cell type or for cells harboring a specific virus. The transformed bone marrow cells might then be treated with 5FC to selectively eliminate (or purge) the transduced cells, after which the treated bone marrow could be introduced into a subject.

Other uses for the CDNSS are not fully described here, including its use as a double negative selection vector and its use as a diagnostic indicator of homologous recombination. Further information regarding these and other applications is available.

A corresponding group of divisional patent applications claiming different aspects of this technology (e.g. a vaccine for mammals against tumors) have also been filed and are available for licensing. (portfolio: Gene-Based Therapies—Therapeutics, vectors, control sequences/genes; Gene-Based Therapies—Therapeutics, vectors, viral)

Dominant Negative Transcription Regulatory Proteins Created by Acidic Amphipathic Alpha-Helical Extension of the Leucine Zipper

Vinson, C.R. (NCI)
Filed 31 Jul 95
Serial No. 60/001,654
Licensing Contact: Allan Kiang, 301/496–7735 ext 270

Members of the transcription factor family of molecules termed basic-region leucine zipper (bZIP) proteins are characterized by the fact that they contain two regions—a hepted repeat of leucine residues (the leucine zipper) and a region rich in basic amino acids. Dimerization with other protein molecules occurs by interactions with the leucine zipper domains allowing interaction of DNA regulatory sequences with the basic domain, thereby stabilizing the dimer. This invention embodies the creation of dominant negative (DN) transcription factors modified to increase the stability of the dimerization reaction between the leucine zipper regions of the bZIP proteins. This results in a DN factor that has the ability to inhibit DNA binding and then transactivation, thereby preventing the production of other proteins or the expression of genes that are detrimental. A transgenic animal model has been produced expressing a DN factor that interacts and inhibits a cellular factor indicating the utility of this approach. (portfolio: Gene-Based Therapies—Therapeutics, other)

Method of Identifying Inhibitors of the Jak-STAT Signal Transduction Pathway

Leonard, W.J. (NHLBI)
DHHS Reference No. E–176–95/0
Licensing Contact: Allan Kiang, 301/496–7735 ext 270

The invention provides identification methods for agents which inhibit the Jak–STAT signaling transduction pathway. Drugs identified by these methods are candidates for the treatment of proliferative disorders dependent on the Jak–STAT pathway, including those caused by HTLV–1. In addition, such agents may be potent immunosuppressive drugs with potential applications not only for organ transplantation but also for treatment of autoimmune diseases. (portfolio: Cancer—Therapeutics, miscellaneous; Internal Medicine—Miscellaneous)

Dated: April 11, 1996.

Barbara M. McGarey, J.D.,

Deputy Director, Office of Technology Transfer.

[FR Doc. 96–9614 Filed 4–18–96; 8:45 am]

BILLING CODE 4140–01–M

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, HHS.

ACTION: Notice.

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 U.S. 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 301/496–7075; fax 301/402–0220). A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

A Gene Encoding a Human Reduced Folate Carrier (RFC) and Methods for the Treatment of Methotrexate-Resistant, Transport-Deficient Cancer Cells

Moscow, J., Cowan, K.H., He, R. (NCI)
Filed 7 Jun 95
Serial Nos. 08/484,840 and 08/483,094
Licensing Contact: Allan Kiang, 301/496–7735 ext 270

Methotrexate (MTX), a folate agonist that inhibits the cellular enzyme dihydrofolate reductase, is effective for the treatment of several types of cancer including non-Hodgkin's lymphoma, childhood acute lymphoblastic leukemia, osteosarcoma, and breast cancer. A major drawback of MTX therapy, however, is that previously responsible tumor cells may become resistant to MTX after continued exposure. Increased expression of the reduced folate carrier (RFC) protein can restore sensitivity to MTX. This intention embodies methods to treat various forms of cancer that have become resistant to MTX by increasing expression of RFC protein in tumor cells via gene therapy, thereby restoring MTX sensitivity. Methods for determining the level of RFC expression, employing antibodies or specific nucleic acid probes, are also described. (portfolio: Cancer—Therapeutics, conventional chemotherapy, other)

Hepatocellular Carcinoma Oncogene

Yang, S.S. (NCI)
Filed 6 Jun 95
Serial No. 08/471,540 [DIV of 08/324,445 which is FWC of 07/575,524 (Aban) which is CIP of 07/451,953 (Aban in favor of FWC 07/774,156, which issued as U.S. Patent No. 5,403,926 4 Apr 95)]
Licensing Contact: Ken Hemby, 301/496–7735 ext 265

Hepatocellular carcinoma is a liver cancer which has high levels of incidence in Asian populations, e.g., China, Korea. Incidence of hepatocellular carcinoma is greater among chronic carriers of hepatitis. A transforming sequence or oncoprotein, hhc^{M} has been identified which is the amplified gene expression product of hepatoma. Antibodies to the hhc^{M} product or the cDNA itself can be used for diagnostic, therapeutic, and screening tests. They may also be used as research tools in studying hepatocellular carcinoma. (portfolio: Cancer—Diagnostics; Cancer—Research Reagents)

Antiproliferative Protein

Nuell, M.J., McClung, J.K., Danner, D.B., Stuart, D. (NIA)
Filed 5 June 95
Serial No. 08/466,762 (CON of 07/612,674)
Licensing Contact: Ken Hemby, 301/496–7056 ext 265

Controlled division is central to proper cellular function. Inability to regulate cell division can lead to uncontrolled growth, such as cancer, or cell death, apoptosis. Cellular proteins that are involved in inhibiting tumor growth, the tumor suppressor genes, have been identified. A second class of negative regulatory genes that when mutated lead to cell death also exist. This invention embodies a member, prohibition, of this second class of genes. Prohibition may be useful for the treatment of unregulated cell growth, cancer. In addition, inactivation of the prohibition gene or its product may be useful for conditions characterized by insufficient cellular proliferation, such as osteoporosis, fragile skin, and poor wound healing. (portfolio: Cancer—Therapeutics)

Method for Treatment of Kaposi's Sarcoma (KS) by Antisense Olingonucleotides

Ensoli, B., Gallo, R.C. (NCI)
Filed 5 Jun 95
Serial No. 08/463,978 (DIV of 08/072,575)
Licensing Contact: Cindy K. Fuchs, 301/496–7735 ext 232

A novel method of blocking the growth of Kaposi's Sarcoma (KS) lesions using antisense oligonucleotides has been developed. This method offers a means to significantly improve the treatment of this condition. KS is a proliferation disease of vascular origin frequently seen in patients infected with the human immunodeficiency virus type-I (HIV–I), the etiologic agent of acquired immunodeficiency syndrome (AIDS). It typically occurs as lesions in the skin and, in more advanced stages, the lesions appear as multiple purplish to brown subcutaneous plaques or nodules. Supernatants from AIDS–KS derived (AIDS–KS) cells have been shown to induce normal endothelial cells to proliferate, degrade and cross the membrane basement, following by migration and organization into tube-like structures. These are the same events that are required for the formation of new blood vessels, or angiogenesis. Furthermore, molecular analysis of the factors produced by AIDS–KS cells revealed that, in particular, mRNA encoding basic fibroblast growth factor (bFGF) is expressed in relatively high quantities and bFGF is indeed responsible for the growth and proliferation of AIDS–KS cells. A number of unique antisense oligonucleotides with high binding affinity for bFGF mRNA are provided which effectively inhibit the progression of AIDS–KS cells in patients. This invention includes a method for administering the treatment as well as for monitoring the progress of KS in a patient. (portfolio: Gene-Based Therapies—Therapeutics, oligonucleotide-base therapies, antisense; Infectious Diseases—Therapeutics, antivirals, AIDS)

Human-Derived Monocyte Attracting Purified Protein Product Useful in a Method of Treating Infection and Neoplasms in a Human Body, and the Cloning of a Full-Length cDNA Thereof

Yoshimura, T., Robinson, E.A., Appella, E., Leonard, E.J. (NCI)
Filed 24 May 95
Serial No. 08/449,552 (DIV of 07/686,264, CON of 07/304,234)
Licensing Contact: Jaconda Wagner, 301/496–7735 ext 284

A novel class of human-derived peptide products offers an important new tool for the treatment of a variety of infections and neoplasms in the human body. Macrophages, which are derived from monocytes, play a central role in human immune response and defense against infection. Previously, no pure human leukocyte-derived monocyte-attracting substance has been isolated. These newly isolated peptide products, which exhibit potent monocyte chemotactic activity, may be helpful in enhancing immune response to a variety of infections as well as cancers. (portfolio: Cancer—Therapeutics)

Retrovirus Vectors Derived From Avian Sarcoma Leukosis Viruses Permitting Transfer of Genes Into Mammalian Cells and Therapeutic Uses Thereof

Barsov, E., Hughes, S.H. (NCI)
Filed 22 may 95

Serial No. 08/445,462
Licensing Contact: Larry Tiffany, 301/496–7056 ext 206

For sensitive applications (like human gene therapy) it has been relatively difficult to develop high titer defective retroviral vector stocks that are routinely and reliably free of recombinant replication competent virus. The new invention, which is based on an avian leukosis virus (ALV) vector, addresses this issue. The new ALV vector has an envelope gene derived from a mammalian retrovirus. The new vector is replication competent in avian cells, so that high titer viral stocks can be prepared simply and rapidly. Although the new vector can efficiently infect mammalian cells, including human cells, the vector is constitutively replication defective in mammalian cells. Since these vectors are incapable of replicating in mammalian cells, they should be safe for a number of sensitive applications, including human gene therapy. (portfolio: Gene-Based Therapies—Therapeutics, vectors, viral)

Human B Lymphotropic Virus (HBLV) Isolation and Products

Salahuddin, S.Z., Ablashi, D.V., Josephs, S.F., Saxinger, W.C., Wong-Staal, F., Gallo, R.C. (NCI)
Filed 22 Feb 95 (priority to 4 Aug 86)
Serial No. 08/392,674
Licensing Contact: George Keller, 301/496–7735 ext 246

This invention concerns the isolation of a new human virus, originally called Human B Lymphotropic Virus (HBLV), now known as Human Herpes Virus Type 6 (HHV–6). HHV–6 causes the common childhood disease roseola. It has been linked to other diseases in persons in an immune deficient state, including those who are HIV infected. Recently it has been linked to multiple sclerosis. The claims cover the virus itself, nucleic acid sequences from the virus and proteins they encode, cell cultures infected with the virus, and detection of the virus by DNA hybridization and immunoassay means. The application was foreign filed, PCT/US87/01815, and has been granted in Europe. (portfolio: Infectious Diseases—Diagnostics, viral; Infectious Diseases—Vaccines, viral; Infectious Diseases—Reagents)

Bistriazenes As Chemotherapeutic Agents

Michejda, C., Blumenstein, J. (NCI)
Filed 12 Sep 94
Serial No. 08/302,480 [CON of 07/786,001, which is CIP of 07/527,915 (both Aban); also related to 08/082,902 filed 28 Jun 93, which is a FWC of 07/527,915]
Licensing Contact: Joseph Contrera, 301/496–7056 ext 244

The bistriazenes are novel alkylating agents which are structurally similar to polyamines, e.g., spermine, which interact with DNA. Most currently employed chemotherapeutic alkylating agents interact with DNA, after which a crosslinking reaction may occur. The bistriazene compounds appear to interact with the DNA, while maintaining structural integrity, only to subsequently decompose on the surface of DNA forming a highly reactive species capable of multi-strand breaks and interstrand crosslinks. This reactivity can be modulated depending on chemical modifications to the bistriazene molecule. These drugs are highly cytotoxic, but their chemical reactivity can be modulated in a highly predictable way. Thus, the bistriazene compounds of this invention represent an entirely novel class of chemotherapeutic alkylating agents, which hold promise for greater specificity and lower toxicity compared to other alkylating agents. (portfolio: Cancer—Therapeutics, vaccines)

Substituted O^6-Benzylguanines and 6(4)-Benzyloxypyrimidines

Moschel, R.C., Pegg, A.E., Dolan, M.E., Chae,M-Y. (NCI)
Filed 1 Aug 94
Serial No. 08/283,953
Licensing Contact: Joseph Contrera, 301/496–7056, ext 244

Inactivation of the human DNA repair protein, O^6-alkylguanine-DNA alkyltransferase leads to a dramatic enhancement in the cytotoxic response of human tumor cells and tumor xenografts to chlorethylating antitumor drugs. This invention embodies a series of compounds that effectively inactivate the alkyltransferase protein. In addition, the claims of this invention provide methods to enhance the chemotherapeutic treatment of tumor cells by treatment with substitutedO^6-benzylguanines and 6(4)-benzyloxypyrimidine derivatives. Invention is co-owned with The University of Illinois at Chicago and Pennsylvania State University. (portfolio: Cancer—Therapeutics, conventional chemotherapy, alkylating agents; Cancer—Therapeutics, conventional chemotherapy, other)

O^6-Substituted Guanine Compositions, and Methods for Depleting O^6-Alkylguanine-DNA Alkyltransferase

Moschel, R.C. (NCI), Dolan, M.E. (Univ. Chicago), Pegg, A.E. (Penn State)
Filed 7 June 94
Serial No. 08/255,190 (CIP of 07/875,438, CIP of 07/805,634, DIV of 07/492,468)
Licensing Contact: Joseph Contrera, 301/496–7056 ext 244

NCI researchers have developed a number of unique derivatives of the purine base, guanine base, guanine, which are particularly useful for increasing the anticancer effects of a wide variety of chemotherapeutic agents. Chemotherapeutic alkylating agents (e.g., chlorethylating nitrosoureas) have some clinical utility against a number of neoplasms but in general have only limited effectiveness in killing tumor cells. This resistance of tumors to the effects of alkylating agents is due in part to the activity of the DNA repair protein, 0^6-alkylguanine-DNA alkyltransferase (AGT), which repairs alkylation damage to the O^6 position of DNA guanine residues. A number of O^6-benzylguanine derivatives have been shown to be effective in depleting AGT. This invention provides additional O^6-benzylguanine compositions which have been shown effective in reducing AGT levels in tumor cell cultures and in enhancing the effectiveness of alkylating agents in tumor-bearing mice. These compounds can be administered with any chemotherapeutic agents with a mechanism of action that involves modification of the O^6 position of DNA quanine residues. (portfolio: Cancer—Therapeutics, conventional chemotherapy, alkylating agents; Cancer—Therapeutics, conventional chemotherapy, other)

ERBB2 Promoter Binding Protein in Neoplastic Disease

Raziuddin and Sarkar, F. (NCI)
Filed 19 Apr 94
Serial No. 08/229,515
Licensing Contact: Susan Rucker, 301/496–7735 ext 245

Isolation of a novel ERBB2 promoter binding protein offers to improve the diagnosis and, specifically, the detection and monitoring of neoplastic diseases. This invention has particular application for the early detection of breast cancer. The HER–2/neu (ERBB2/c-erbB–2), or ERBB2, gene sequence appears to be one of the primary genes responsible for the transition of normal epithelial cells toward carcinoma and the subsequent development of invasive and metastatic cancer. For women, early detection of breast cancer is crucial for survival; however, by the time the gene product of ERBB2 is measurable by current methods, the prognosis of patients is not good. This invention improves on earlier methods for

detecting and treating breast cancer by providing a purified and isolated DNA binding protein that specifically binds to the promoter region of the c-ERBB2 (HER–2/neu) gene sequence (hence the term HER–2 promoter binding protein, HPBF). Antibodies specific for this DNA binding protein, called HPBF, can be used to assay for the presence of HPBF in a biological sample and, thus, detect the presence of cancer. The purified HPBF also can be used to test the ability of substances to inhibit the activity of HPBF and thus potentially halt or reverse growth of the cancer. This invention includes antisense nucleotides that effectively prevent HPBF from binding to the promoter. (portfolio: Cancer—Therapeutics, biological response modifiers, growth factors)

Acridone-Derived Bisintercalators as Chemotherapeutic Agents

Michejda, C.J., Cholody, W.M. Hernandez, L. (NCI)
Filed 14 Mar 94
Serial No. 08/213,315
Licensing Contact: Joseph Contrera, 301/496–7056 ext 244

This invention describes a noval class of acridone-derived intercalating agents that offer to improve the treatment of certain cancers. Presently available anti-tumor agents often have great toxicity for normal cells as well as tumor cells. Therefore, there is a great need for new chemotherapeutic agents that selectively kill tumor cells while sparing healthy cells. A number of acridine-based compounds have recently been discovered that exhibit high anti-tumor activity. This newly developed class of acridone-derived agents, which bind strongly to nucleic acids, have potent cytotoxic activity which is selective for solid tumor cells, especially for colon and prostatic tumors. Because some of these compounds exhibit enhanced fluorescence when bound to DNA, they also may be used in assays for the detection of DNA. (portfolio: Cancer—Therapeutics)

Dated: April 11, 1996.

Barbara M. McGarey,

Office of Technology Transfer.

[FR Doc. 96–9615 Filed 4–18–96; 8:45 am]

BILLING CODE 4140–01–M

Notice of Meeting of the NIH Director's Advisory Panel on Clinical Research

Notice is hereby given that the NIH Director's Advisory Panel on Clinical Research, a group reporting to the Advisory Committee to the Director (ACD), National Institutes of Health (NIH), will meet in public session in Wilson Hall, third floor of the Shannon Building (Building 1) National Institutes of Health, Bethesda, Maryland 20892, on May 16, 1996 from 8:30 a.m. until approximately noon.

The goal of the Panel is to review the status of clinical research in the United States, and to make recommendations to the ACD about how to ensure its effective continuance. Topics to be considered at this meeting are subcommittee progress reports and a discussion of the proposed NIH Clinical Research Center.

Attendance may be limited to seat availability. If you plan to attend the meeting as an observer or if you wish additional information, please contact Mrs. Janet Smith, National Institutes of Health, Building 10, Room 1C–116, 10 Center Drive, MSC 1154, Bethesda, Maryland 10892–1154, telephone (301) 402–3444, fax (301) 402–3443, by May 6, 1996. Individuals who plan to attend and need special assistance, such as sign language interpretation or other special accommodations, should contact Ms. Smith in advance of the meeting.

Dated: April 10, 1996.

Ruth L. Kirschstein,

Deputy Director, NIH.

[FR Doc. 96–9616 Filed 4–18–96; 8:45 am]

BILLING CODE 4140–01–M

Public Health Service

National Toxicology Program; National Toxicology Program (NTP) Board of Scientific Counselors' Biennial Report on Carcinogens (BRC) Subcommittee Meeting

Pursuant to Public Law 92–463, notice is hereby given of a meeting of the National Toxicology Program (NTP) Board of Scientific Counselors' Biennial Report on Carcinogens (BRC) Subcommittee, U.S. Public Health Service, in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences (NIEHS), 111 Alexander Drive, Research Triangle Park, North Carolina, on May 8, 1996.

The primary agenda topic will be concerned with the discussion of the process for listing or delisting substances in the Biennial Report on Carcinogens (BRC) (formerly Annual Report on Carcinogens (ARC)).

The preliminary agenda topics with approximate times are as follows:

8:30 a.m.–8:45 a.m.—Report of the Director, NTP
8:45 a.m.–9:00 a.m.—Report of the Director, Environmental Toxicology Program (ETP)
9:00 a.m.–10:00 a.m.—Report on the background history of the BRC
10:15 a.m.–11:15 a.m.—Presentation and discussion of the process for listing or delisting substances in the BRC
11:15 a.m.–11:35 a.m.—Report from the NIEHS/NTP BRC Review Group
11:35 a.m.–12:00 p.m.—Report from the NTP Executive Committee Working Group for the BRC
1:00 p.m. –2:00 p.m.—Subcommittee discussion of BRC presentations
2:00 p.m.–3:00 p.m.—Presentation of select chemicals previously approved for listing in the 8th and 9th BRC to compare application of proposed BRC criteria with previous ARC selection criteria
3:15 p.m.–4:30 p.m.—Subcommittee discussion of BRC review responsibilities
Adjournment

Public Comments Encouraged

The meeting is open to the public. A brief summary of the review of the BRC criteria for listing or delisting substances is available on request from the NTP Liaison Office, P.O. Box 12233, MD B3–01, Research Triangle Park, NC 27709, phone: (919) 541–0530, FAX: (919) 541–0295. Brief public oral comments will be allowed at appropriate times during the meeting. Registration to attend is not required; however, to ensure adequate seating, we ask that those planning to attend let us know. To register, receive information on the agenda, or be put on the mailing list for summary minutes subsequent to the meeting, please contact: Dr. L.G. Hart, P.O. Box 12233, Research Triangle Park, NC 27709; telephone: (919) 541–3971; FAX: (919) 541–0719.

Dated: April 12, 1996.

Kenneth Olden,

Director, National Toxicology Program.

[FR Doc. 96–9617 Filed 4–18–96; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No. FR–3917–N–66]

Office of the Assistant Secretary for Public and Indian Housing: Notice of Proposed Information Collection for Public Comment

AGENCY: Office of the Assistant Secretary for Public and Indian Housing, HUD.

ACTION: Notice.

SUMMARY: The proposed information collection requirement described below