of NAT in human hepatocytes, e.g., para-amino salicylate (PAS) for NAT1 and dichlorphenamide for NAT2, which can be used either in chemoprevention of cancer or in conjunction with a chemotherapeutic which metabolizes NAT, potentially resulting in reduced toxicity to the patient. Since these inhibitors are currently-marketed drugs, clinical development can be accelerated, and pilot studies are already underway.

Methods for Inhibiting Chaperone Proteins

Monica G. Marcu, Leonard M. Neckers, Theodor W. Schulte (NCI)
Serial No. 60/124,135 filed 12 Mar 99

This technology describes the use of an antibiotic, Novobiocin, that has been used clinically in people for many years. This compound and structural analogues such as chlorobiocin and coumermycin A1, which are coumarins, have been discovered to bind to Heat Shock Protein 90 (Hsp90), resulting in the destabilization and proteolytic degradation of a number of proteins whose function and stability depend on their association with Hsp90. These proteins include oncogenic kinases such as Raf, Her2/neu(erbB2), and Src, and transcription factors such as mutant p53. Novobiocin has demonstrated an ability to deplete Raf from the spleens of mice, suggesting that it may have anti-Hsp90 biologic properties in humans. Novobiocin and its analogues are an improvement on currently known chemotherapeutics such as geldanamycin because these compounds lack both a quinone and a macrocycle in their chemical structure and are thus better tolerated and less toxic to humans at high dosages.

Identification of The Geldanamycins as Inhibitors of The HGF/SF–Met–uPA Proteolytic Network

Craig Webb, Curtis Hose, Anne P. Monks, George F. Vande Woude, Edward A. Sausville (NCI)
Serial No. 60/119,114 filed 08 Feb 99

This technology describes a class of compounds (Geldanamycins) as important inhibitors to the HGF–SF–Met–uPA–plasmin signaling pathway. Considerable evidence demonstrates that the HGF–SF–Met pathway plays a significant role in the etiology of human cancers and the formation of secondary metastases. These compounds have the ability to revert certain transformed phenotypes through down regulation of the expression of the Met receptor at subnanomolar concentrations. Thus, these compounds could have utility in the treatment and therapy of invasive human cancers where the HGF–SF–Met pathway is implicated.

Food Quality Indicator Device

Dwight W. Miller, Jon G. Wilkes, Eric D. Conte (FDA)
DHHS Reference No. E–093–97/1 filed 16 Jul 98

The invention is a device which indicates the quality of frozen food by colorimetrically detecting bases generated by decomposition. The food quality indicator consists of a paper strip or other insert support treated with proprietary compounds for detection at temperatures below zero degree C of Bacteriological and/or enzymatic food decomposition. It operates without thawing frozen foods, and for excellent application for seafoods such as shrimp, fish as well as red meat.

Sensitive Assay for Measuring Gallium Levels in Body Tissues and Fluids

Edward Reed, Kang B. Lee (NCI)
Serial No. 08/355,153 filed 08 Dec 94; U.S. Patent 5,650,627 issued 22 Jul 97

A sensitive assay method for measuring the quantity of elemental gallium present in a test sample comprising a body tissue or body fluid. The method involves a test sample after diluting with nitric acid to be introduced into atomic absorption spectrometer having a Zeeman-effect background correction capability. Sample absorption to be determined at a desired wavelength while subjecting the test sample to an atomization and a burning in an atomic spectrometer. A correction of Zeeman effect to be made on the said determined absorption and comparing corrected absorption for the test sample with a standard curve.

Dated: May 28, 1999.

Jack Spiegel,

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

[FR Doc. 99–14376 Filed 6–4–99; 8:45 am]

BILLING CODE 4140–01–M

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.

N-Acylphosphoramidites and Their Use in Oligonucleotide Synthesis

Serge Beaucage et al. (FDA)
DHHS Reference No. E–031–98/0 filed 24 Mar 99
Licensing Contact: Charles Maynard; 301/496–7735 ext. 243; e-mail: cm251n@nih.gov

This technology relates to the synthesis of oligonucleotides, and intermediates useful in its synthesis. The therapeutic application of oligonucleotides is based on the selective formation of hybrids between antisense oligonucleotides and complimentary nucleic acids, such as messenger RNAs. Such hybrids inhibit gene expression by blocking protein translation. Successful inhibition of gene expression requires the antisense oligonucleotide to be nuclease resistant so that it can be successfully transported through biological membranes and can hybridize selectively to a target complementary nucleic acid, thereby actively blocking protein translation.

This present invention of synthesizing polymers has tremendous synthetic advantages that are unprecedented with respect to the synthesis of oligonucleotides in that it enables the facile production of P-chiral oligomeric or polymeric products, with complete control of stereochemistry with respect to the phosphorous atom.

Identification and Use of High Efficacy Vaccine Antigens

Ronald N. Germain (NIAID), Irena Stefanova (NIAID), Roland Martin (NINDS), Marco Vergelli (NINDS), Bernhard Hemmer (NINDS)
Serial No. 60/124,064 filed 12 Mar 99
Licensing Contact: Richard U. Rodriguez; 301/496–7056 ext. 287; e-mail: rr154z@nih.gov

The invention relates to the identification and use of high efficacy

antigens or immunogens. Antigen-specific or adaptive immunity in higher vertebrates is mediated by limphoid effector cells, T and B-lymphocytes. T-lymphocytes have αβ-receptors (TCR) that recognize ligands comprised of cell-surface molecules encoded in the major histocompatibility complex (MHC) bound to short peptide fragments of protein antigens. These antigen-specific effector T-lymphocytes are involved in resistance to infections, in anti-tumor immunity and in autoimmune-diseases. Studies have shown that activation of the TCR by a peptide-MHC complex triggers an intracellular biochemical signaling cascade. These studies have also shown that different peptide-MHC complexes can yield different levels of responses, thus affecting the effectiveness of an immune response to various disease states. The inventors provide methods to efficiently identify optimized or heteroclitic-ligands (superagonists) which would have utility in the formation of anti-cancer and anti-pathogen vaccines with enhanced potency compared to the natural self- or foreign peptide ligand. This is achieved by a ''biochemical fingerprinting'' process that involves the analysis of various phosphorylation patterns elicited in specific T-cells by TCR activation using peptide-MHC complexes. These patterns enable direct identification of how optimal a given ligand is for the test T-cells. When the initial ligand proves suboptimal by this technique, improved ligands can be identified by making variants of the original peptide, and then analyzing the phosphorylation patterns elicited by these variants until an optimal pattern is achieved. In this manner, specific peptides can be tested until a ''superagonist'' is isolated and development of this ''superagonist'' as a potential vaccine can proceed. These methods provide a direct evaluation of the immunologic ''quality'' of an initial vaccine candidate. Their use should greatly reduce the number of potential antigen-candidates that need to be researched and focus important resources on antigen-candidates with superior potential to succeed.

Polymorphic Human $GABA_A$ Receptor Alpha-6 Subunit

Drs. Nakao Iwata, David Goldman, and Mark Shuckit (NIAAA)
DHHS Reference Number E–061–98/0 filed 19 Fed 99
Licensing Contact: Marlene Shinn; 301/496–7056 ext. 285; e-mail: ms482m@nih.gov

Human heritability studies using twins and adoptees have indicated that alcoholism is a complex disorder having a genetic component. Studies of Children of Alcoholics (COA) have determined that there is a differential decrease in sensitivity to benzodiazepine drugs (BZD) and ethanol within this specific population.

G-Aminobutryric Acid (GABA) receptors are implicated in various neurological and psychiatric disorders. There are two major types of GABA receptors: A, which is associated with a $C1^-$ Channel; and B, which is associated with K^+ and Ca^{2+} channels. Differential expression of individual subunits of the multimeric protein appears to provide a mechanism for the body to convey different physiological functions. the α subunit displays benzodiazepine activity and the α_6 subunit has been associated with alcohol related activity. A proline to serine substitution at amino acid position 385 in the α_6 subunit of the $GABA_A$ receptor within the COA population has displayed a statistical correlation to the average smooth pursuit eye movement after diazepam administration.

The point mutation can be used as a genetic marker to investigate susceptibility to alcoholism as well as the biochemical and physiological responses to both pre- and post-treatment with benzodiazepines. It is also useful in the investigation of psychiatric disorders such as schizophrenia, affective disorder, or anxiety disorders in which abnormal function of the GABAergic neuronal system is implicated.

A Method of Immunizing Humans Against Salmonella Typhi Using a Vi-rEPA Conjugate Vaccine

Zuzana Kossaczka, Shousun C. Szu and John B. Robbins (NICHD) DHHS Reference No. E–020–99/0 filed 04 Dec 98 (PCT/US98/25746)
Licensing Contact: Robert Benson; 301/496–7056 ext. 267; e-mail: rb20m@nih.gov

This invention is a method of immunizing against typhoid fever using a conjugate vaccine comprising the capsular polysaccharide of *Salmonella typhi,* VI, conjugated through an adipic dihydrazide linker to nontoxic recombinant exoprotein A (rEPA) from *Pseudomonas aeruginosa.* The three licensed vaccines against typhoid fever, attenuated *S. typhi* Ty21a, killed whole cell vaccines and Vi polysaccharide, have limited efficacy, in particular for children under 5 years of age, which make an improved vaccine desirable.

It is generally recognized that an effective vaccine against *Salmonella typhi* is one that increases serum anti-Vi IgG eight-fold six weeks after immunization. The conjugate vaccine of the invention increases anti-Vi IgG, 48-fold, 252-fold and 400-fold in adults, in 5–14 years-old and 2–4 years-old children, respectively. Thus this is a highly effective vaccine suitable for children and should find utility in endemic regions and as a traveler's vaccine. The route of administration can also be combined with routine immunization. The synthesis of the conjugates, not including the superior clinical results, is described in Infection & Immunity 65(7), pp. 2088–2093, June 1997.

Antagonists Of The αEβ7 Integrin As Therapeutic Agents For Inflammatory Diseases

Bjorn R. Ludviksson, Warren Strober, Rolf Ehrhardt (NIAID) Serial No. 60/019,957 filed 25 Nov 98
Licensing Contact: Richard U. Rodriguez; 301/496–7056 ext. 287; e-mail: rr154z@nih.gov

The disclosed invention relates to a method of treating and/or preventing the inflammatory response of an autoimmune disease, an allergic disease, a graft-versus-host disease and a transplantation rejection. In particular, this treatment or prevention is accomplished by administering antagonists of the $\alpha^E\beta7$ integrin. $\alpha^E\beta7$ is expressed on intra-epithelial lymphocytes (IELs) and on lamina propria (LP) lymphocytes. $\alpha^E\beta7$ can be upregulated by TGF–β, and it is speculated to have regulatory functions such as homing or retention. The pathogensis of chronic intestinal inflammation may depend on the traffic of lymphocytes from sites of induction to sites of inflammation. The inventors have shown that chronic intestinal inflammation can be prevented and reversed in an IL–2 $-/-$ murine model. Administration of anti-$\alpha^E\beta7$ prevents colonic inflammation and reverses pre-existing inflammation. Therefore, this technology can be used to treat, prevent or reverse inflammatory conditions as well as providing a method of screening for substances effective in reducing the inflammatory effects of $\alpha^E\beta7$.

Methods And Compositions for HDL Holoparticle Uptake Receptor Insertion

B Brewer Jr., AT Remaley, S Argraves (NHLBI) DHHS Reference No. E–204–98/0 filed 15 May 98
Licensing Contact: Charles Maynard; 301/496–7735 ext. 243; e-mail: cm251n@nih.gov

This technology relates to compositions and methods for a high density lipoprotein (HDL) holoparticle uptake receptor. This receptor is used in the identification and development of substances (therapeutic agents) which modulate the activity and/or expression

of the receptor, thereby modulating the uptake of HDL by cells expressing the receptor on the cell surface.

HDL has anti-atherogenic properties and is known to inhibit oxidation of low density kiporprotein (LDL). Transgenic animals having elevated levels of HDL are resistant to high cholesterol dieto-induced atherosclerosis. Therefore, understanding factors which influence plasma levels of HDL, such as mechanisms of HDL metabolism, is of major importance.

The present invention makes a significant contribution to the art by providing an HDL holoparticle uptake receptor comprising a complex of proteins and screening methods for identifying substances that modulate the activity and/or expression of the receptor.

Modified HCV Peptide Vaccine

Jay A. Berzofsky (NCI), Pablo Sarobe (NCI), CD Pendleton (NCI), Stephen M. Feinstone (FDA)
Serila No. 60/-97,446 filed 21 Aug 98
Licensing Contact: J. Peter Kim; 301/496–7056 ext. 264; e-mail: jk141n@nih.gov

Hepatitis C virus (HCV) is a single stranded RNA virus responsible for the majority of non-A non-B hepatitis. Hepatitis C virus (HCV) has a worldwide distribution and is a major cause of liver cirrhosis and hepatocellular carcinoma in the U.S., Europe, and Japan. For this reason, development of a vaccine against hepatitis C is of great importance.

The present invention provides immunogenic peptides of HCV core protein which elicit an enhanced immune response, methods for making these pepetides, and methods for using these peotides for a variety of therapeutic, diagnostic, and prognostic applications, including a vaccine. More specifically, the present invention provides an isolated peptide, and isolated HCV core polypeptide, a fragment of an HCV core polypeptide and nucleic acids which encode the peptides and polypeptides of this invention. The invention provides a modified HCV core peptide that is more immunogenic than the corresponding natural core peptide for eliciting human cytotoxic T lymphocytes.

Conformationally Locked Nucleoside Analogues

Inventors: Victor E. Marquez, Juan B. Rodriguez, Marc C. Nicklaus, Joseph J. Barchi, Jr., Maqbool A. Siddiqui (NCI)
U.S. Patent Numbers: 5,869,666 (filed March 14, 1997); 5,629,454 (filed September 23, 1994, with priority back to September 24, 1993)
Foreign Filing: PCT/US94/10794 (issued as European Patent Number 0720604 and Australian Patent Number 677441)

Conformationally Locked Nucleoside Analogs As Antiherpetic Agents

Inventors: Victor E. Marquez, Juan B. Rodriguez, Marc C. Nicklaus, Joseph J. Barchi, Jr., Maqbool A. Siddiqui (NCI)
U.S. Patent Number: 5,840,728 (filed August 7, 1997, with priority back to August 7, 1996)
Licensing Contact: Peter Soukas; 301/496–7056 ext. 268; e-mail: ps193c@nih.gove

The compounds of the present invention represent the first examples of carbocyclic dedeoxynucleosides that in solution exist locked in a defined N-geometry (C3′-endo) conformation typical of conventional nucleosides. These analogues exhibit increased stability due to the substitution of carbon for oxygen in the ribose ring. The invention includes 4′-6′-cyclopropane fused carbocyclic dideoxynucleosides, 2′-deoxynucleosides and ribonucleosides as well as oligonucleotides derived from these analogues; the preferred embodiment of the invention is carbocyclic-4′-6′-cyclopropane-fused analogues of dideoxypurines, dideoxypyrimidines, deoxypurines, deoxypyrimidines, purine ribonucleosides and pyrimidine ribonucleosides. In addition, oligonucleotides derived from one or more of the nucleosides in combination with the naturally occurring nucleosides are within the scope of the present invention.

The second invention discloses a method for the treatment of herpes virus infections by the administration of cyclopropanated carbocyclic 2′-deoxynucleosides to an affected individual. This invention is a method of administration of the compounds described above. The compounds of this invention are particularly efficacious against herpes simplex viruses 1 and 2 (HSV–1 and HSV–2), Epstein-Barr Virus (EBV) and human cytomegalovirus (CMV), although the nucleoside analogues of the invention may be used to treat any condition caused by a herpes virus. Specifically, the N-methanocarba-T (Thymidine) analogue has been shown to exhibit strong activity against HSV–1 and HSV–2, and moderate to strong activity against EBV. Significantly, the anti-HSV activity of the Thymidine analogue is stronger than that of Acyclovir (shown in a plaque reduction assay), a widely used anti-HSV therapeutic. Furthermore, the Thymidine analogue is also non-toxic against stationary cells and is potent against rapidly dividing cells. Dosage amounts for the compounds are similar to those of Acyclovir.

Descriptions of the inventions may be found in Rodriguez et al., J. Medicinal Chemistry 37:3389 3399 (1994) and Marquez et al., J. Medicinal Chemistry 39:3739–3747 (1996).

Dated: May 28, 1999.

Jack Spiegel,

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

[FR Doc. 99–14377 Filed 6–4–99; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; 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 meeting of the National Cancer Advisory Board.

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. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2). The grant applications and/or contract proposals 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 and/or contract proposals, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Cancer Advisory Board.

Date: June 8, 1999.

Open: June 8, 1999, 8:30 a.m. to 4:00 p.m.

Agenda: Report of the Director, NCI; Reports and Presentations Related to NCI Administrative and Program Developments; Presentations and Discussions Related to Special Populations and Quality of Care Issues; NCI Clinical Research Opportunities; NCAB Subcommittee Meeting and NCAB Working Group Report; Legislative and National Cancer Statistic Updates.

Place: Building 31, C Wing, 6 Floor, Conference Room 10, National Institutes of Health, 3100 Center Drive, Bethesda, MD 20892.