is also problematic because commonly used assays based on detecting marker gene expression do not provide accurate biodistribution data due to failure to obtain a signal in those tissues in which the marker gene is not expressed. This invention obviates these deficiencies by disclosing the use of triplex-forming oligonucleotides (TFO) which bind to their target sequences in circular plasmid DNA and thereby creating stable readily detectable triplex-complexes when introduced into living eukaryotic cells. These fluorescent or radio-labeled polypurine TFOs can provide a noninvasive way to study the biodistribution of a plasmid of interest in vivo using tools developed for probe detection and radiolabeling. In summary, this technology allows one to quantitatively monitor the whole-body distribution of labeled-vectors in living animals or patients.

**Extension of a Protein-Protein Interaction Surface To Inactivate the Function of a Cellular Protein**

CR Vinson, D Krylov (NCI), DHHS Reference No. E – 113-95/1 filed 29 May 96, Related cases: Serial No. 08/690,111 filed 31 Jul 96; PCT/US96/12590 filed 31 Jul 96.

This invention uses sequence-specific DNA binding proteins as eukaryotic transcription factors, i.e., transcription regulatory proteins. Specifically, multimeric proteins having nucleic acid (DNA or RNA) binding domains in which the binding domain or protein interaction surface is engineered or modified to be acidic in nature. The acidic nature of the protein increases the stability of heteromultimeric or heterodimeric complexes that are formed. This type of nucleic acid binding protein should be capable of regulating the function of a target nucleic acid sequence or gene to which it is bound, thereby acting as a potent dominant-negative regulator of gene transcription, cell growth and cell proliferation. These proteins could be useful as drugs, inhibitory molecules or growth-controlling agents that can inhibit the expression, and thus the activity, of cellular proteins which have harmful, deleterious and even lethal effects on cell growth and survival. These proteins could also be used in gene therapy by using appropriate constructs to allow expression of a regulatory protein to treat suitable disease states. The constructs could also be used to create transgenic animals or plants in which the dominant-negative protein interacts with the wild-type protein to provide viable phenotypes to evaluate and assess the in vivo effects of the protein. In summary, this technology provides for useful tools and therapeutics which are capable of regulating specific target gene expression and gene-product activity.

**Dated:** February 16, 1999.

**Jack Spiegel,** Director, Division of Technology Development and Transfer, Office of Technology Transfer. [FR Doc. 99-4659 Filed 2-24-99; 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.

**ADDRESS:** 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.

**Activity Dependent Neurotrophic Factor III (ADNP)**

DE Brenneman (NICHD), Ilana Gozes (Tel Aviv University)

M Bassan

Serial No. 09/187,330 filed 06 Nov 1998 and claiming priority to PCT/US98/02485 and 60/037,404, Licensing Contact: Susan S. Rucker; 301/496-7056 ext. 245; e-mail: sr156v@nih.gov

These application(s) disclose the identification, isolation, cloning and sequencing of a newly discovered gene which encodes a protein known as ADNF III (Activity Dependent Neurotrophic Factor III)/ADNP (Activity Dependent Neuroprotective Protein). The gene has been localized to the long arm of chromosome 20 at 20q13.2—a region which has previously been associated with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). In addition to describing ADNF III/ADNP, the applications describe an eight (8) amino acid peptide fragment NAP which is an active region ADNF III/ADNP.

ADNP and NAP exhibit neuroprotective activity, the ability to protect neurons from cell death, with an EC50 in femtomolar range. Neuronal cell death is suggested as one mechanism in operation in Alzheimer’s disease making ADNP or NAP attractive as candidates for the development of therapeutics for prevention or treatment of Alzheimer’s disease. Early work using a apo-E deficient mice indicates that NAP can ameliorate learning and memory deficiencies normally exhibited in these mice. Other diseases involving neuronal cell death where ADNP or NAP may be useful include stroke, Huntington’s disease, epilepsy, Parkinson’s disease and Tourette’s syndrome.

**A Mutant Of TEV Protease That Is Resistant To Autoinactivation**

David S. Waugh (NCI)

Serial No. 60/304,799 filed 19 Oct 98 Licensing Contact: Kai Chen; 301/496-7056 ext. 247; e-mail: kc169a@nih.gov

This invention concerns a mutant of the tobacco etch virus (TEV) protease. Due to its high degree of sequence specificity, the TEV protease is valuable reagent for cleaving fusion proteins. However, the wild-type TEV protease also cleaves itself to yield a truncated enzyme with greatly reduced proteolytic activity. As a result, more protease must be used to achieve complete digestion of a fusion protein substrate, and the stability of the enzyme during long term storage becomes problematic. This invention provides a means of avoiding autoinactivation of TEV, thereby enhancing its utility as a reagent for cleaving fusion proteins at a specific, predetermined site.

**Fluorescent Pteridine Adenosine Analogs As DNA Probes Not Requiring Separation of Products**

ME Hawkins, FM Balis, WPflederer (NCI)

Serial No. 60/099,487 filed 08 Sep 98 Licensing Contact: Manja Blazer; 301/496-7056 ext. 224; e-mail: mb379e@nih.gov

These are part of a series of nucleic acid analogs to be used as fluorescent probes for DNA analysis. Their site-specific incorporation into DNA through a deoxyribose linkage causes them to be much more sensitive to changes in the DNA than traditional fluorophores.
Incorporated through automated DNA synthesizers, these probes are affected by base stacking and therefore are excellent detectors of binding, cleavage and configurational changes brought about by interactions with proteins or other DNA. This property makes them useful in the following commercial applications:

- Study of DNA/DNA and DNA/protein interactions
- Detection of positive PCR products without the use of radioactive isotopes and gels

Highly Selective Butyrcholinesterase Inhibitors For The Treatment And Diagnosis Of Alzheimer's Disease And Dementias

NH Greg, A Brossi, TT Soncrant, Q Yu, M Hausman (NIA)

DHHS Reference No. E-247-97/1 filed 09 Jul 98 (CIP of Provisional U.S. Patent Application No. 60/052,087 filed 09 Jul 97)

Licensing Contact: Leopold J. Luberecki, Jr.; 301/496-7735 ext. 223; e-mail: 1187a@nih.gov

Defects in the cholinergic system have been reported to primarily underlie memory impairments associated with normal aging and with Alzheimer’s disease (AD). This invention describes compounds that are selective, long-acting and reversible inhibitors of the enzyme butyrylcholinesterase, BChE, that readily enter the brain to both improve cognitive performance and reduce levels of β-amyloid precursor protein for the treatment of AD. Specific cholinergic pathways within the brain are regulated by BChE, rather than by its sister enzyme acetylcholinesterase, AChE, that regulates the vast majority. Selective BChE inhibitors, described within this invention, substantially improve cognitive performance in animals without the classical peripheral and central side effects associated with cholinesterase inhibition. They, additionally, reduce levels of β-amyloid precursor protein, the source of the toxic peptide, β-amyloid, which is elevated in the brain of patients with AD. Since small populations of people entirely lack BChE activity and yet live normally healthy lives, complete inhibition of BChE can be sustained without harm. In addition to therapeutics, analogues of compounds described in the invention can be used as potential early diagnostics of AD.

Unlike AChE, which is substantially reduced early in AD, levels of BChE are increased, particularly in areas associated with deposits of β-amyloid. The high, selective binding of compounds of this invention to BChE provides the means to image and quantitate the enzyme as a marker of AD and disease progression. Hence, the compounds described in this invention have both therapeutic and diagnostic potential for AD.

Novel Nitric Oxide-Releasing Amidine- and Enamine-Derived Diazieniumdiolates, Compositions and Uses Thereof and Method of Making Same

JA Hrabie, LK Kefer (NCI)

DHHS Reference No. E-067-97/1 filed 01 Jul 98 (based on Provisional U.S. Patent Application No. 60/051,690 filed 03 Jul 97)

Licensing Contact: Leopold J. Luberecki, Jr.; 301/496-7735 ext. 223; e-mail: 1187a@nih.gov

Diazieniumdiolates are compounds that contain an N2O2 functional group. These compounds are potentially useful as produgs because they generate nitric oxide upon degradation. Nitric oxide (NO) plays a role in regulation of blood pressure, inflammation, neurotransmission, macrophage-induced cytostasis, and cytotoxicity. NO is also important in the protection of the gastric mucosa, relaxation of smooth muscle, and control of the aggregation state of blood cells. A series of amidine- and enamine-derived diazeniumdiolates have been produced that offer many advantages over previously known derivatives.

For example, these derivatives are not expected to decompose into carcinogenic nitrosamines and exhibit a full range of solubility in water. Many of these derivatives are more heat stable than previous analogs and release NO at a slow rate. Additionally, some of these compounds are insoluble in water and thus coatings prepared from them may not secrete component material after NO release. These properties may make these derivatives suitable for coating medical devices, stents, and implants to take advantage of the anti-coagulant properties of NO. The newly developed synthetic scheme also allows for the production of NO-release agents from known pharmaceuticals. Using enamines, it may be possible to incorporate the actions of three pharmaceuticals into a single agent, one as a carbonyl compound, another as an amine, and the third as the NO-releasing diazeniumdiolate. Overall, these compounds appear to be applicable toward the wide variety of processes involving nitric oxide.

Therapeutic And Prophylactic Uses Of Sucrose Octasulfate

Thomas C. Quinn (NIAID), Manuel A. Navia

Serial No. 60/076,314 filed 27 Feb 98

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

This invention claims methods for the use of sucrose octasulfate against gonorrhea and chlamydia infections. Furthermore, the invention claims compositions combining sources of octasulfate with antibacterial or anti-infective agents. Prior to this invention, sucrose octasulfate (FDA approved) has been widely used as an anti-ulcerant. The methods described in the application are characterized by one or more of the following advantages: (1) sucrose octasulfate minimizes disruption of the epithelial cell surface to which it is applied; (2) sucrose octasulfate has little, if any, toxic or tumorigenic effects; (3) sucrose octasulfate has little, if any, anticoagulant activities (in contrast to larger anionic sulfated polysaccharides), contraceptive effects, or other reproductive or teratogenic effects; (4) sucrose octasulfate has affinity for damaged epithelium, which is known to be the preferred site for bacterial entry; and (5) sucrose octasulfate forms non-covalent gels, or remains in a liquid state depending upon the particular salt used. The absence of contraceptive and/or teratogenic activity demonstrated for sucralfa to date makes this compound ideal for use in preventing sexually transmitted infections such as chlamydia or gonorrhea. In vitro studies have been completed on the effects of sucrose octasulfate against chlamydia and gonorrhea.

O-Linked GlcNAc Transferase (OGT): Cloning, Molecular Expression, and Methods of Use

JA Hanover, W Lubas (NIDDK)

DHHS Reference No. E-128-97/0 filed 31 Mar 97

Licensing Contract: Manja Blazer; 301/496-7056 ext. 224; e-mail: mb379@nih.gov

This technology relates to a post-translational modification of a protein involving the addition of N-acetylgalactosamine in O-glycosidic linkage to serine or threonine residues in cytoplasmic and nuclear proteins. It is believed that such modification plays a significant role in regulating the activity of proteins involved in transcriptional and translational processes. It likely represents a novel signal transduction pathway. In particular, this invention provides an enzyme catalyzing the formation of these derivatives, uridine diphospho-N-acetylgalactosaminyl transferase (O-GlcNAc transferase (O-GlcNAc, OGT), and a nucleic acid encoding the system.
The invention also modifies many phosphoproteins that are components of multimeric complexes. The sites modified by O-linked GlcNAc often resemble phosphorylation sites, leading to a suggestion that the modification may compete for substrate in these polypeptides. Based on the above properties, this technology may be useful in the following ways:

- As a terminal component of the hexosamine biosynthetic pathway, OGT may be a key target for systemic problems with glucose homeostasis such as diabetes mellitus.
- Model for glucose sensing by the pancreatic beta cell.
- Model for the study of OGT role in regulating oncogene activity and function.
- Screen for various tumors correlating OGT activity with metastatic potential.
- Tumor suppressor activity and the involvement of OGT in transcriptional dysregulation during transformation.


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

[FR Doc. 99–4660 Filed 2–24–99; 8:45 am]
BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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AGENCY: National Institutes of Health, Public Health Service, DHHS.

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Attenuated and Dominant Negative Variant cDNAs of Stat6: Stat6b and Stat6c

WJ LaRochelle, BKR Patel, JH Pierce (NCI)
PCT/US98/17821 filed 27 Aug 1998 and based on applications 60/070,397 and 60/056,075.

These application(s) disclose the identification, isolation, cloning and sequencing of two distinct variants of Stat6. The variants or isoforms of human Stat6 are designated Stat6b and Stat6c and they are, respectively, attenuated and dominant negative isoforms of Stat6. The Stat6 proteins are a family of signal transduction molecules which have been shown to play a role in modulating the activity of a variety of cytokines. In particular, Stat6b has been shown to be involved in interleukin-4 (IL-4) regulation suggesting that Stat6 may play a role in inflammatory and cell-mediated immune responses. The dominant negative isoform, Stat6c, is particularly interesting because of its ability to down-regulate the IL-4 response. This suggest that it may be useful alone or in identifying agents which may be useful in treating diseases linked to the IL-4 response such as asthma. Diagnostic applications for allergy or asthma may also be possible. In addition to describing the variants of Stat6 the application describes the promoter for Stat6 and notes that the gene is located on the long arm of chromosome 12 at 12q13.3–14.1. Regulation of the Stat6 promoter might provide insight toward the control of proliferative and inflammatory processes.


Methods and Compositions for Treatment of Restenosis

AB Mukherjee, GC Kunde, DK Panda (NICHHD)

DHHS Reference No. E–163–96/1 filed 07 Aug 98 (PCT/US98/16569) and claiming priority to 60/054,694 filed 07 Aug 97

This application describes the use of antisense oligonucleotides designed to inhibit osteopontin production, and their use in treating restenosis, the reocclusion of an artery following angioplasty. Utilizing blood samples and coronary artery tissues from patients it was demonstrated that OPN levels are increased both in the atherosclerotic tissues as well as in the blood following angioplasty. Further, using an in vitro system employing human coronary artery smooth muscle cell culture (CASMC), it has been demonstrated that these antisense molecules inhibit osteopontin expression.

This work has been published in PNAS USA 94(19):9308–13 (August 18, 1997).

cDNA for a Human Gene Deleted in Liver Cancer

BZ Yuan, NC Popescu, SS Thorgeirsson (NCI)

Serial No. 60/075,952 filed 25 Feb 98

This application discloses the identification, isolation, cloning and sequencing of a newly discovered gene, DLC-1 (Deleted in Liver Cancer), which has been localized to the short arm of chromosome 8 at 8p21.3–22 using FISH (fluorescent in situ hybridization). Studies of human tumors show that DLC-1 is deleted in 50% of primary hepatocellular carcinomas and is not expressed in 20% of hepatocellular carcinoma cell lines. This differential expression suggests that diagnostic applications of DLC-1 may be developed. Other cancers where preliminary data indicates that DLC-1 may have diagnostic possibilities are breast and colon cancer. A polyclonal antibody which recognizes DLC-1 has been characterized. Work to date indicates that DLC-1 is a tumor suppressor gene suggesting that gene therapy utilizing DLC-1 may also be possible.

This work has appeared, in part, in Cancer Research 58(10): 2196–9 (May 15, 1998).

Partial Intron Sequence of Von Hippel-Lindau (VHL) Disease Gene and Its Use in Diagnosis of Disease

WM Linehan, M1 Lerman, FS Latif, B Zbar (NCI)

Serial No. 08/623,428 filed 28 Mar 96

This application, in conjunction with patents 5,654,138 (8/5/1997) and 5,759,790 (6/2/1997), describes the isolation, cloning, and sequencing of the gene associated with Von Hippel Lindau (VHL) syndrome. The sequence of VHL includes, in addition to the coding region, the sequence of the VHL promoter and genomic sequence information at the intron/exon boundaries of the VHL gene. The VHL gene is found on the short arm of chromosome 3 at 3p25–26. It functions as a tumor suppressor and has been associated with sporadic kidney cancer,