



Office of Patents and Licensing Research Tools

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Method for Making Hormone Heterodimer (*William Moyle, RWJMS 97-07*) Research Tool

Background

The glycoprotein hormones are a group of heterodimeric glycoproteins produced in the anterior pituitary gland and include luteinizing hormone (LH), follicle stimulating hormone (FSH) and thyroid stimulating hormone (TSH). These hormones are also found as excretion products in human urine. Significant quantities of human chorionic gonadotropin (hCG) hormone are found in the urine of pregnant women and LH and FSH are found in the urine of menopausal women. Deglycosylated hormone analogs and hormone analogs with prolonged half-lives or universal activities are useful in many clinical and commercial applications but are difficult to produce. For example, female infertility caused by high LH activity could be suppressed by the administration of hormone analogs that inhibit endogenous LH activity. However, the preparation of biologically active hormone is often impeded by changes to its native structure. The present invention describes a method for the preparation of heterodimeric hormone analogs.

Description of the Technology

Glycoprotein hormones comprise of a common alpha subunit and a hormone specific beta subunit. The substitution of the alpha subunit of one hormone with that of another does not alter the receptor binding properties of the recombined hormone while, the substitution of the beta subunit of one hormone with that of another alters the receptor binding specificity of the hormone. The crystal structure of hCG revealed that both alpha and beta subunits contain a cysteine-knot architecture. The present invention discloses a method for the preparation of a cysteine knot protein containing an alpha and a beta subunit resulting in biologically active heterodimeric protein analog. Specifically, the method involves attaching a dimerization domain to the amino termini of both alpha and beta subunit of a cysteine knot protein followed by dimerization of the subunits to form a heterodimeric protein analog. Alternatively, the heterodimeric protein analog can be made by attaching a dimerization domain to the amino termini of the alpha subunit and c-terminus of the beta subunit of a cysteine knot protein followed by dimerization of the subunits to form a heterodimeric protein analog. This method can be used to dimerize any cysteine knot proteins such as TGFbeta, PDGF, NGF, Veg1, bone morphogenic proteins, activin, and inhibin.

Advantages & Applications

- The method described in this invention can be used to dimerize any cysteine knot protein such as TGFbeta, PDGF, NGF, Veg1, BMPs, activin, and inhibin.
- This strategy can be utilized in the preparation of any heterodimeric analog of glycoprotein hormones including hCG/hFSH and hCG/hTSH chimeras, and truncated glycoprotein hormone subunits
- The heterodimers produced by this method retain the properties of the native hormone.

Patent Status

United States patent US 6,486,303 B1 was granted on November 6, 2002

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Novel Method for the Production of Heat Shock Proteins (*Hewitt, RWJ 00-38*)
Research Tools

Background

Heat shock proteins (HSPs) are a family of highly conserved proteins produced in response to a variety of stressful conditions such as injury, disease, nutrient deprivation, inflammation and infection. HSPs also play a major role in normal cellular functions by maintaining homeostasis, and as “chaperones” ensuring the proper folding of proteins. HSPs have been implicated in a variety of diseases including autoimmune and inflammatory diseases such as rheumatoid arthritis, scleroderma, and SLE. They are also known to confer drug resistance to cancer cells thereby interfering with cancer treatment. HSPs are able to elicit an immune response against tumor cells, which is attributed to the unique tumor specific antigenic peptides that are bound to HSPs. Therefore heat shock proteins may have therapeutic applications as vaccines in the treatment of a variety of diseases. **Thus there is a need to purify patient-specific heat shock proteins in large quantities for the generation of customized vaccines.**

Description of the Technology

Heat shock proteins are produced by treating the subject tissue in a manner that initiates coagulative necrotic changes. This is accomplished by heating the subject tissue at a predefined temperature. The tissue is then cooled and incubated in a growth medium and HSPs are collected from the supernatant. The method described in the invention results in the inexpensive production of heat shock proteins that can be separated and purified. The advantages of the present method, is its low-cost and ease of scalability. Resultant HSPs are produced rapidly and in their native form.

Applications

- Research and Diagnostics
- Vaccine development since the heat shock proteins produced by the method disclosed in the invention may be conjugated to antigens and used in the preparation of vaccines for therapeutics and prevention of diseases.

Patent Status

PCT application published on August 14, 2003; Publication No.: WO 03/066092 A1.

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Super-Tat Proteins for use in Research, Diagnostic and Therapeutic Applications
(*Mathews, NJMS 01-03*) Research Tools

Background

The human immunodeficiency virus (HIV) Tat protein stimulates the expression of early genes of the virus. Tat protein also interacts with cellular transcriptional factors and cytokines and alters the expression of a variety of genes in HIV-1-infected and non-infected cells. Tat function requires its binding to (P-TEFb), a cellular positive transcription elongation factor b. Tat protein is secreted by HIV infected cells and extracellular Tat has been implicated in the progression of AIDS. Also, extracellular Tat exerts a variety of pleiotropic effects on target cells by binding to cell surface receptors such as VEGF, and chemokine receptors. For example, extracellular Tat has been shown to act on quiescent CD4 cells rendering them susceptible to HIV infection. Thus, inhibition of extracellular Tat represents a viable approach to stem the progression of AIDS. Variants of Tat protein, with enhanced or reduced activity, would be useful tools in advancing the current knowledge of HIV replication, pathogenesis, and progression of AIDS. **The present invention relates to new variants of the Tat protein that exhibit higher transcriptional activation than wild-type TAT.**

Description of the Technology

New variants of the wild-type Tat were generated via site directed mutagenesis of a single amino acid. The new variants exhibit 5-fold higher transcription activation and 3.5-fold higher P-TEFb binding activity than wild-type Tat. The enhanced P-TEFb binding and transcription activation of Super-Tats would enable the use of lower levels of the protein in research and clinical applications, thereby minimizing the toxic side effects known to be associated with the use of high doses of wild-type Tat.

Applications

- As a research tool to study viral replication for HIV
- In therapeutic applications including the inhibition of viral transcription
- For the production of antibodies for vaccine development
- For the preparation of conditioned medium from cells expressing Super-Tats -for use in diagnostic assays to detect HIV infection
- For synthesis of Super-Tats for activation of latent HIV

Patent Status

PCT application published on September 4, 2003. Publication No.: WO 03/072709.

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Novel Fluorescent Probes for Labeling Proteins and Nucleic Acids (*Laskin, RWJ 01-09*) *Research Tools*

Background

Fluorescent probes or fluorophores are routinely used to detect and quantify biomolecules such as proteins and nucleic acids. There are several fluorophores available. Among these are thiol reactive probes such as BODIPY, fluorescein, Oregon Green, tetramethylrhodamine and Texas Red that are used to selectively label proteins and peptides at thiol functional groups. However, their use is restricted to thiol containing biomolecules. Coumarin derivatives have also been used as fluorophores when emission in the blue-green fluorescent region is desired. However, coumarin derivatives are insoluble in aqueous solutions and fluorescence is quenched upon conjugation to proteins. Psoralens (furocoumarins) routinely used in cosmetics and in treatment of skin disorders such as psoriasis and eczema can also be used to label DNA and RNA. Psoralens label DNA and RNA by intercalating into the double stranded structure and covalently binding to pyrimidines. However, their fluorescence is quenched in reactions requiring prolonged use of the probe. **The present technology describes various derivatives of dihydropsoresalen compounds that can be used to label both proteins and nucleic acids. These compounds can be used in reactions requiring intensely fluorescent signals in extended use.**

Description of the Technology

The derivatives of dihydropsoresalen compounds described in this invention are thiol reactive and produce highly fluorescent products. It was shown that the fluorescent product generated during labeling of a thiol-containing molecule, retains the ability to intercalate into any nucleic acid. This property enables the use of these products to detect biomolecules that do not contain thiol groups such as nucleic acids. Thus, dihydropsoresalen compounds and derivatives can be used to detect very small quantities of both nucleic acids and proteins in biological samples. The feasibility of using dihydropsoresalen compounds and derivatives for labeling proteins and nucleic acids was demonstrated using BSA and glutathione.

Applications

- Labeling proteins and nucleic acids for research and clinical diagnostics

Patent Status

United States patent application published on 01/29/04 (Pub. No.: US-2004-0018517 A1)

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A Novel Enzyme for Use in Labeling Biomolecules (*Laskin, RWJ 01-19*) Research Tools

Background

In molecular biology and immunohistochemistochemical applications, alkaline phosphatase and peroxidase enzymes are routinely used to detect and estimate DNA, RNA and proteins through the measurement of chemifluorescence or chemiluminescence of end products. However, peroxidase applications require the use of hydrogen peroxide as a cofactor and alkaline phosphatase yields high background. Another enzyme, catalase, has also been used in some of the industrial and research applications described above. This enzyme has peroxidase (oxidization of alcohols in the presence of hydrogen peroxide) and catalytic (breakdown of hydrogen peroxide to oxygen and water) activities. However the peroxidase activity requires addition of horseradish peroxidase and hydrogen peroxide, and the end-point used to detect catalase activity entails the monitoring a decrease in fluorescence, which compromises sensitivity of the assay. **The present technology represents significant improvement in currently used nucleic acid and protein assays and detection systems. Novel fluorescent probes and methods for their use in research applications are described.**

Description of the Technology

It was discovered that the mammalian enzyme catalase has a unique oxidase activity in the presence of certain substrates. This enables the exploitation of this enzyme to oxidize a number of non-fluorescent substrates to produce intensely fluorescent end-products without requirement for hydrogen peroxide as a co-factor. Also, the oxidase activity of the enzyme could be competitively inhibited by certain substrates of the enzyme. The optimum conditions and kinetics of the reaction have been deciphered for AMPLEX-RED and DCFH-DA substrate. It was also discovered that the fluorescent signal could be amplified under certain experimental conditions. Methods and techniques for enhancing the fluorescent signal have been worked out.

Applications

- Nucleic acid analysis in gene profiling, sequencing, Southern and Northern blots
- Protein analysis in Western blotting, ELISA, immunohistochemistry
- In industrial applications: preparation of hair coloring products; detergents for stain removal; paper production industry for removal of excess dyes and inks and for bleaching printed paper; textile industry for removal of excess dyes; to produce gelled products in agriculture, pharmaceutical and personal care industry; in wood industry to produce fiber boards; as an antimicrobial or antiviral agent

Patent Status

United States patent application published on 12/11/03 (US-2003-0228648-A1)

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A Three Dimensional Matrix for Producing Living Tissue Equivalents (*Hewitt, RWJ 01-35*) Research Tools

Background

Tissue or organ injury or loss due to disease or accident results in tremendous health care costs. Tissue injury such as burns, diabetic foot ulcers, and venous leg ulcers require immediate medical attention. However, treatment of these conditions is heavily limited by the availability of donor organs and tissues. Furthermore, the success of organ transplantation is often limited by tissue rejection and risk of disease transmission. An autologous tissue replacement, comprised of the patient's own cells, or an allogenic tissue replacement, may solve the problem of tissue and organ deficiency, but these strategies pose certain limitations that are yet to be overcome. Thus, tissue equivalents that are close to native human tissue in histological and functional properties would be desirable in treating tissue and organ injuries. **The present invention satisfies the need for producing tissue equivalents that have utility in a wide variety of medical applications.**

Description of the Technology

UMDNJ researchers have developed a method for producing *de novo* a three-dimensional collagen matrix using human fibroblast cells for use as tissue equivalents. The matrix disclosed in the invention can be used to construct living tissue equivalents such as skin, blood vessel, bone tendon, ligaments and organ equivalents. For example, a three dimensional collagen matrix can be produced by including fibroblasts in a hemostatic clot mixture consisting of blood plasma and thrombin. The fibroblasts polymerize and cross link to produce an insoluble fibrin matrix permitting the fibroblast to proliferate and produce collagen. Furthermore, the characteristics of the matrix may be altered to suit individual's specific needs. For example, tissue may be formed in any desired shape or size by embedding a scaffolding material. Other tissues can also be produced using the method disclosed in the invention.

Applications

- Therapeutic applications: to replace lost or damaged tissues.
- Research: to test efficacy of investigational agents; to study disease mechanisms; to test efficacy of treatment protocols; to culture cells such as keratinocytes, hepatocytes, bone marrow cells

Patent Status

United States application published on 09/04/2003 (US-2003-0166274-A1)

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A Rapid Method for Purification of Ubiquitinated Proteins (*Madura, RWJ 01-47*)
Research Tools

Background

The ubiquitin/proteasome complex is the major intracellular non-lysosomal proteolytic system that catalyzes the degradation of many regulatory proteins. Ubiquitin is a highly conserved protein present in all eukaryotes. Conjugation of ubiquitin molecules to proteins marks them for degradation via the ubiquitin/proteasome pathway. Critical regulators of cell growth, differentiation, apoptosis and tumor suppression are targets of this proteolytic pathway, and include p53, β -catenin, c-Jun, c-Myc, I κ B α and Bcl2. The presence of ubiquitinated proteins is often one of the hallmarks of pathological conditions such as neurodegenerative diseases and cancer. Purification of ubiquitinated proteins would enable further research into disease pathogenesis ultimately leading to novel therapeutic developments. **The present invention describes a method to selectively isolate ubiquitinated proteins involved in critical cellular events.**

Description of the Technology

A protein (more specifically, a protein domain) critical to eukaryotic DNA excision repair mechanism was shown to bind ubiquitinated proteins. This binding affinity was exploited to prepare an affinity matrix by coupling the ubiquitin-binding protein directly to Sepharose beads. This affinity matrix represents a very efficient tool to selectively purify ubiquitinated proteins from any target sample in amounts sufficient for further analyses. A Kit for the purification and recovery of ubiquitinated proteins has been developed.

Applications

- For the isolation of low abundance cellular regulatory proteins.
- To test if a protein is a substrate of the ubiquitin/proteasome pathway.
- To generate antibodies against the purified proteins.

Patent Status

PCT application filed and published on 06/19/2003 (Publication No.: WO 03/049602)

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Gaussian Mixture Based Method for Missing Value Estimation in Microarray (*Welsh, RWJ 03-14*) *Research Tools*

Background

DNA microarray technology is extensively used for the generation of gene expression data from different cell lines and disease tissues. The expression levels of thousands of genes can be assayed in a single chip. Clustering is routinely used in the analysis of microarray data, whereby genes with similar expression profiles can be identified. Clustering could also be used to classify disease tissues. The distance among entities is measured using the Pearson correlation coefficient, the Spearman rank correlation coefficient, and inner product. However, missing entries arising from blemishes on the microarray often complicate the measurement of the distances. Thus, it is critical to determine the values of missing entries in performing cluster analysis.

Description of the Technology

UMDNJ researchers have designed a method to estimate the value of missing entries based on Gaussian Mixture modeling. This method consists of clustering microarray data using a Gaussian mixture clustering model and estimating missing values by a GMCimpute algorithm. This method has been found to be empirically more accurate than existing methods such as K nearest neighbor method, the singular value decomposition method, and the spine fitting method.

Applications

- To estimate the values of missing entries in microarray data.

Patent Status

PCT patent application filed. (Application No.: PCT/US2004/024351)

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Efficient Gene Transfer into Lymphocytes (*Dougherty, RWJ 93-10 & 94-28*) Research Tools

Background

Introduction of exogenous genes into primary B lymphocytes has therapeutic potential for the treatment of diseases that affect B cell compartment, such as X-linked agammaglobulinemia, and genetic diseases such as hemophilia and lipoprotein lipase deficiency. The antigen presenting function of B cell would be especially useful in augmenting anti-tumor or anti-viral immune response. Several gene therapy protocols involving retroviral mediated gene transfer into lymphocytes are currently being used. Many of these protocols rely on long-term *in vitro* expansion of cells and drug selection of stably infected cells. These protocols are not suitable for introduction of exogenous genes into B cells as they require long-term expansion of cells *in vitro*, resulting in loss of homing patterns upon introduction of cells into the host. **The present invention provides a protocol for transferring exogenous genes into primary lymphocytes without the need for drug selection of stably infected cells.**

Description of the Technology

Scientists at UMDNJ have devised a protocol for the efficient transfer of exogenous genes into primary lymphocytes. The primary steps involve the stimulation of enriched lymphoid subpopulation with growth factors specific to the subpopulation to induce proliferation of the cells followed by co-culturing the stimulated cells with helper cell line that is infected with a retroviral vector. Greater than 90% of the lymphocytes produced using this protocol, are enriched for the provirus with one to five copies of the exogenous gene per cell. Furthermore, the transferred gene is expressed at high levels in the infected cells. This protocol is rapid as it eliminates the selection step required by other methods to enrich for the target population of cells that express the exogenous gene. As a result, the homing properties of the cells are not compromised upon their introduction into the host.

Applications

- To transfer of genes into lymphoid cells
- For the treatment of genetic disorders involving lymphocytes.

Patent Status

Three United States patents granted on September 16, 1997, and November 11, 1997, and May 25, 1999 (Patent Numbers: 5,667,998, 5,686,280 and 5,906,928)

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HIV-1 Vectors (*Rabson & Strair, RWJ 93-11*) Research Tools

Background

HIV-1 long terminal repeat (LTR) enhancer/promoter sequences are required for the replication of HIV in T cell lines. Previous studies have demonstrated that mutations in these regions alter HIV tropism. Efficient HIV RNA expression requires both the interaction of virally-encoded Tat protein with the TAR region of HIV RNA and the interaction of cellular transcription factors, such as Sp1 and NF-Kappa-B, with LTR DNA. Deletion of both the binding sites for Sp1 and NF-Kappa-B factors results in the loss of HIV-1 replicative ability, while alterations in the binding sites of one of the factors has variable effects on HIV-1 replication depending on the cell type and the level of the transcription factor. Thus, alterations in the binding sites of cellular transcription factors present in LTR region affect the range of cell types that HIV can infect. Thus, cytopathic viruses can be genetically altered to induce specificity. **The present invention describes the derivation of a genetically altered HIV-1 vector that can be used to selectively destroy tumor cells.**

Description of the Technology

Scientists at UMDNJ have developed a genetically altered human immunodeficiency virus type 1 (HIV-1) vector that replicates only in human tumor cells, specifically, in CD4+ cells expressing Tax protein of Human T-cell Lymphotropic Virus Type I (HTLV-I). The HIV-1 LTR and enhancer sequences have been replaced by two copies of the HTLV-I LTR 21 base pair repeat Tax responsive element (TRE). The introduction of TRE into HIV-1 LTR imparts to the HIV-1 vector the ability to replicate in HTLV-1 expressing cells, but not in CD4+ cells lacking HTLV-I Tax. Additionally, this invention describes a method for killing HTLV-1 infected cells in humans with HTLV-1 disease using the genetically engineered human HIV-1 vector.

Applications

- As research tools
- Genetically altered HIV-1 encoding toxic products would be useful as cytotoxic agents for treating diseases caused by HTLV-1

Patent Status

United States Patent Number 5,837,512 granted on November 17, 1998

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Long Term Maintenance of Lymphocytes *in vitro* (Ron & Dougherty, RWJ 93-43)
Research Tools & HIV

Background

Normal un-stimulated human peripheral T lymphocytes have numerous pharmacological, diagnostic and research applications. Examples include the study of T cell biology and HIV infection of T cells, and gene therapy applications. Maintenance of T lymphocytes *in vitro* requires the activation of T cells with either an antigen or mitogen followed by expansion of the cells with cytokines. However, the T cells maintained in this fashion are often specific for a particular antigen and are not suitable for studying T cell biology. **The present invention provides a culturing system for the long-term maintenance of primary resting T lymphocytes *in vitro* without the requirement for stimulation with cytokines or antigens.**

Description of the Technology

UMDNJ scientists have developed an *in vitro* culture system for the long-term maintenance of primary, human peripheral blood and umbilical cord blood T lymphocytes. The procedure involves the development of a monolayer of adherent cells from human peripheral blood or umbilical cord blood that can support the maintenance of non-adherent resting mature T cells. The adherent cells, some resembling macrophages, can be developed within a week of starting the culture and can support the maintenance of resting mature T cells for up to three months. The T cells maintained in the culture system of the present invention retain the ability to respond to mitogens and allogeneic cells.

Applications

- For the long term maintenance of primary, human peripheral blood and umbilical cord blood T lymphocytes
- To study HIV infection of T cells
- For research applications
- For pharmacological, clinical and diagnostic applications used in gene therapy applications.

Patent Status

United States Patent Number: 5,688,915 granted on November 18, 1997

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Opioid Receptor Knockout Mice (*Pintar, CABM 96-17, 96-31, 96-32, and 98-11*)
Research Tools

Background

Morphine, endogenous opioid peptides and certain opioid drugs exert a pleiotropism of biological effects ranging from stress response to pain, reproductive behavior, and feeding behavior through binding to endogenous receptors called opioid receptors. There are three major types of well characterized opioid receptors: δ , κ , and μ . Many of the opiate analgesics modulate pain perception through μ opioid receptor. However, their use is limited by side effects such as constipation and the potential to develop dependence on opioids. δ receptor agonists modulate pain perception without the development of dependence and thus, these receptors are useful targets in the development of novel analgesics. **The present technology relates to animal models that can be used to uncover novel pathways and targets for the development of agents capable of modulating stress response, pain and feeding.**

Description of the Technology

Knockout mice with disruptions in the δ , κ , and μ opioid receptors and two genes that encode several opioid receptor ligands were generated. Certain μ and δ receptor agonists have been shown to exert analgesic effects in both δ and μ receptor single and double knock-out mice suggesting that there are additional pathways that mediate analgesia. Additionally, studies with δ knockout mice identified a novel pathway that modulates pain perception without the development of analgesic tolerance. These novel pathways represent additional targets for the development of non-opioid analgesics for the management of chronic pain as well as to overcome analgesic tolerance and thus the potential for their abuse. In another set of experiments, these mutant mice were used to study agents that affect food intake and obesity. These studies have revealed that an intact opioid system is necessary for the effective management of feeding behavior. Thus, opioid system could serve as target for the control of feeding behavior, and management of obesity and obesity related diseases.

Applications

- To study the role of opioid receptors in pain perception, drug and alcohol abuse
- To identify novel targets for non-opioid analgesics
- To identify compounds or agents, that modulate appetite, stress, anxiety and pain

Patent Status

Unpatented technology

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Nitric Oxide Synthase Inhibitors (*Laskin, RWJ 98-23*) *Research Tools & Oncology*

Background

Nitric oxide synthase (NOS) - mediated diseases include sunburn, rheumatoid arthritis, ulcerative colitis, Crohn's disease, septic and toxic shock, asthma, hypertension, myocarditis, diabetes and autoimmune and respiratory disorders. Nitric oxide is synthesized via the arginine to citrulline deamination pathway making this pathway a target for the design of therapeutic drugs. The literature describes various N- γ -substituted arginines as inhibitors of NOS.

Description of the Technology

This invention relates to a novel class of planar, fused-ring bio-isoteric models of arginine as NOS inhibitors. The synthesis, structure, and utility of eight novel members of triazole families that inhibit NOS have been described. One of the compounds when tested on mammalian PAM 212 cancer cells showed antiproliferative property.

Applications

- For use as NOS inhibitors in diseases requiring inhibition of NOS
- Anticancer agents

Patent Status

United States patent application 10/863,785 was filed in 2004

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Combination Rack for Chemical Analyzers (*Jekelis 99-43*) Research Tools

Description of the Technology

This invention pertains to the ornamental design for a combination rack for chemical analyzers.

Patent Status

United States Patent Number US D469, 027 S granted on January 1, 2003

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mRNA Capping Enzymes (Shatkin 97-20) Research Tools

Background

Most messenger RNAs contain a 5' terminal m7G cap that is added to nascent pre-mRNAs by capping enzymes. Capping of mRNA transcripts occurs in three steps: 1) removal of γ phosphate from the 5' end by RNA triphosphatase 2) transfer of GMP from GTP by guanylyl-transferase and 3) addition of a methyl group to the N7 position of the guanine cap by methyl-transferase. The capping enzymes in lower and higher eukaryotes differ in structure and catalytic mechanism. Lower eukaryotes have separate triphosphatase, guanylyltransferase and methyltransferase components. Higher eukaryotes including humans and other metazoans have a bi-functional capping enzyme consisting of triphosphatase and guanylyl-transferase and a separate methyl-transferase. The mRNA cap is critical for completion and processing of RNA polymerase II transcripts and for their transport to the cytoplasm. The cap enhances mRNA stability and facilitates proper initiation of translation. **The present technology relates to a mammalian capping enzyme complex comprising mRNA guanylyl-transferase and mRNA methyl-transferase.**

Description of the Technology

Vectors containing the cDNAs encoding a mammalian capping enzyme and methyl-transferase have been made. The capping enzyme complex has been shown to catalyze the formation of 5' terminal cap. The guanine-7-methyltransferase enzyme has been demonstrated to catalyze the formation of methylated 5' terminal cap. A method for the correct formation of 5' ends on mRNA transcripts using these enzymes has been standardized, and kits for each of these reactions can be readily developed. Additionally, the enzymes have been used in coupled transcription-translation experiments in cell free extracts for the formation of RNA 5' capped transcript followed by translation of the capped transcript. Kits for generating proteins from a DNA template and from an uncapped mRNA template in cell free extracts using these enzymes can also be developed.

Applications

- For making mRNA transcripts with correct 5' ends
- Inhibition of RNA degradation
- Purification of intact mRNAs using antibodies to the cap
- For labeling RNAs
- Coupled transcription translation reactions for producing proteins in cell free extracts.
- Structural and mechanistic differences between human and fungal (also parasite) capping apparatus make it an attractive target for anti-fungal (also anti-malarial, anti-trypanosomal) drug discovery. The capping enzyme is essential for cell viability and thus can be used for screening inhibitors of the components of capping enzyme complex.
- For use in complementation assays to identify and screen genetic defects in capping pathway

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IL-4 *In-Situ* Staining (*William C. Gause, NJMS 06-14*) *Research Tool*

Background

IL-4 is one of the characteristic cytokines of the Th2, a CD4⁺ effector T cell. Detection of IL-4 *in vivo* has proven difficult due to low expression levels and has required the use of robust and indirect techniques, including real-time fluorogenic RT-PCR, intracellular staining, and ELISPOT assays. These methodologies, while useful, require the disruption of tissue architecture, thereby obscuring analysis of specific micro-environmental expression of the cytokine.

Description of the Technology

The present invention discloses a novel strategy for detecting IL-4 protein *in situ* that amplifies the detection signal enough to be assayed using fluorescent microscopy. This technique employs standard immunohistochemical methods, and allows the detection of IL-4 while maintaining the structural integrity of the tissue, thus permitting the study of protein expression in specific cellular populations.

Applications

- As a research tool to study specific IL-4 expression *in-situ*.
- As a method to study expression of other proteins with low-expression *in-situ*

Patent Status

United States Provisional Application – March 2006.

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Heterocyclic Bibenzimidazole Agents for Enhanced Imaging and Quantification of DNA (*LaVoie, Pilch RWJ 06-35*) Research Tools

Background

Terbenzimidazoles can bind to the minor groove of DNA and they are Topo I inhibitors. They also have significant fluorescent properties. Their strong tendency to self-aggregate has limited their utility as cancer chemotherapeutics. This property makes formulation very difficult and limits absorption and distribution into tumors. Investigators at Rutgers University and UMDNJ determined that the presences of the terminal Benzimidazole, as well as the presence of a 5-phenyl substituent and a 2'-trifluoromethyl group, were associated with an increased potential for self-aggregation. Thus, new Bibenzimidazoles were developed wherein the terminal Benzimidazole was replaced with a different Heterocyclic substituent.

Description of Technology

Novel Heterocyclic Bibenzimidazoles with reduced propensity for self-aggregation and enhanced DNA binding have been identified. These compounds enter into cells very efficiently and bind chromosomal DNA *in vivo* with excellent efficacy and specificity. They are 1,000-fold more sensitive than current agents used for imaging chromosome in cells.

Applications

- These new compounds can be used to image chromosome in cells, nuclear staining, flow cytometry, quantification of DNA, and DNA staining in gels.

Patent Status

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Mouse Model of Invasive Bladder Cancer (*Cory Abate-Shen, 06-38 UMDNJ*) *Research Tool*

Background

Despite significant improvements in diagnosis and treatment, neoplasia of the bladder continues to result in significant mortality. Bladder cancers range from being benign to highly aggressive, and most are epithelial in origin and urothelial in nature. They are believed to arise from two distinct precursor lesions, namely, a papillary form (called Papillary Urothelial Neoplasm of Low Malignant Potential or PUNLMP) and carcinoma-in-situ (CIT). However, it is not well understood how these precursors relate to each other or to benign versus invasive disease. The present invention is a double knockout mouse to be used as animal models for bladder cancer.

Description of the Technology

The present invention is an autochthonous mouse model of bladder cancer that originates in the urothelium and ultimately progresses to invasive disease. This was accomplished by using adenovirus-Cre delivery system to achieve sporadic deletion of tumor suppressor function specifically in the bladder urothelium. Simultaneous deletion of two tumor suppressor genes leads to the development of invasive bladder tumors with 100% penetrance by 4 months, including distant metastases to the liver and other tissues, which are also sites for bladder cancer metastases in humans. The histological appearance of these tumors is remarkably similar to invasive human bladder cancer.

Applications

- This invention provides a tool for identifying therapeutic agents, method of observing the effects of treatment, and an animal model for the development of bladder disease, not limited to cancer.

Patent Status

United States Provisional Application – 2006.

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A Highly Sensitive and Specific System for Large-scale Gene Expression Profiling
(Li, RWJ 06-64) *Research Tools*

Background

High-throughput gene expression profiling is a powerful tool to analyze mRNA expression patterns on a genomic scale in normal and disease tissues. Until now the major limitation for this technology was the need for large amount of RNA for each assay.

Description of the Technology

The novel technology allows the co-amplification of more than 1000 mRNA species using gene-specific primers from as few as a single cell, followed by microarray analysis with probes hybridizing to neighboring exons. Using this assay, differentially expressed genes in normal and disease tissue can be reliably identified. The technology is simple, highly reproducible, specific, and sensitive.

Applications

- Research Market. The technology can be used to study changes in gene expression that occurs in normal biological processes and disease. The technology also can be used in drug discovery and development, biomarker identification, and target selection.
- Molecular Diagnostics. The technology can be used in the diagnosis and prognosis of disease, to determine pre-disposition to disease, to personalize and monitor response to treatment, and many others clinical applications.

Patent Status

United States Provisional Application for Patent was filed.

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Method for Assaying and Inhibiting Activity of Growth-Differentiation Factor-3
(Shen, RWJ 05-53)

Background

Growth-Differentiation Factor-3 (GDF3) is a soluble ligand of the Transforming Growth Factor-*beta* (TGF β) family. **This invention relates to (1) production of active GDF3 protein in mammalian cell culture, (2) a cell culture-based assay for GDF3 activity, and (3) a means to inhibit GDF3 activity.**

Description of the Technology

The assay claimed in this technology relies upon reconstitution of the essential signaling components Cripto, FoxH1, Nodal, GDF1, GDF3, and/or Lefty1 and Lefty2. The signaling activity of these components can be detected using the activin/Nodal-responsive luciferase reporter *A3-luc*. In order to enable efficient production and processing of GDF3, the prodomain of GDF3 has been replaced and a FLAG or V5 epitope tag added to the N-terminus of the GDF3 ligand. The resulting fusion protein has been shown by Western blotting to be expressed and processed efficiently. Co-transfection of the signaling components into 293T cells results in signaling activity and can be detected through the luciferase reporter assay. Co-expression of Lefty1 with other signaling components inhibits signaling activity of the GDF3 ligand.

Applications

- The method described in this invention can be used to study modulators of the signaling pathway by TGF β family members, specifically GDF3.
- The method can be used to screen for novel inhibitors (chemical or antibody-based) of GDF3 activity, which can lead to the identification of a pharmaceutical product that can block obesity induced by high-fat diet.

Patent Status

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3D Bioluminescence (*Dimitris Metaxas, Rutgers University & Debabrata Banerjee, UMDNJ*) *Research Tools*

Background

Bioluminescence imaging (BLI) is an emerging technique for sensitive and non-invasive imaging, which can be used for monitoring molecular events in intact living animals. The increasing use of BLI as the choice of small-animal imaging modality is based on the need for repeated imaging of the same animal transplanted with gene-marked cells. Other imaging modalities such as mPET, MRI are unsuitable for repeated imaging in a laboratory setting as they require sophisticated equipment or radioactive isotope use. The present technology provides a method that allows one to recover 3D tumor locations and their 3D shape from 2D bioluminescence images, then register using proprietary software and visualize the reconstructed tumor with detailed animal geometry extracted from microCT anatomical images.

Description of the Technology

Previous attempts to obtain a 3D shape and tumor location were based on setting up multiple cameras. The present technology provides a method that requires the use of a single CCD camera and a proprietary software algorithm that is rooted in the stereoscopy algorithm in Computer Vision capable of recovering and reconstructing 3D depth and surface information of interesting structures such as tumors from 2D planar images taken by the camera. Experimental results using both phantom and real studies on small animals successfully demonstrated the effectiveness of the present methodology.

Applications and Advantages

- As a research tool for optical imaging of small animals
- Provides a simpler, more general and robust method for 3D bioluminescence than existing technologies

Patent Status

United States Provisional Application – 2005.

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Novel Episomal Expression Vector for Protein Expression (*Cesar E. Guerra & Harvey L. Ozer, NJMS 03-11*) Research Tool

Background

Many plasmid vectors are currently available for expression in mammalian cells. These are generally used for either transient expression of the target gene or, alternatively, for stable transfection to achieve sustained gene expression. Vectors for transient expression require a strong promoter and a convenient cloning site; while vectors for stable transfection must have a selection marker and require plasmid integration into the host genome post-transfection. This event is relatively rare and is rate-limiting, as well as, subject to the vagaries of each particular site of integration. A small number of vectors derived from Epstein-Barr virus (EBV) are capable of autonomous replication and are termed Mammalian Artificial Chromosomes (MACs). Still, a significant need still exists for more flexible, yet powerful expression vectors capable of producing stable transfectants. There is also a need for efficient non-viral gene delivery systems for many transgenic applications and in gene therapy. The disclosed invention, a novel episomal vector design, has the desired characteristics to meet these needs.

Description of the Technology

The present invention relates to the use of a new class of episomal vectors called “Eplus vectors” for stable transfection of mammalian cells. Compared to other vectors derived from the Epstein-Barr Virus and to conventional integrating vectors, Eplus vectors show higher transfection efficiencies, more vigorous growth of transfectants and higher expression levels of genes of interest. Eplus vectors can be used for many applications such as cloned gene expression/regulation, consisting of large genomic clones; recombinant protein over-expression, cDNA clones; stem cell engineering/transgenics; non-viral gene therapy; and DNA vaccines/immunogen production.

Applications

- As a research tool for stable transfection of mammalian cells
- As an industrial tool for robust over-expression of proteins
- For non-viral gene delivery
- For stem cell engineering/transgenics

Patent Status

United States Provisional Application – 2006.

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Miniature Tissue Culture System (*Samuel Lieber & Stephen Vatner, NJMS 06-09*)
Research Tool

Background

Currently there is great interest in using Tissue Engineering techniques and Gene Therapy towards the treatment of disease and dysfunction. The development of these concepts, however, requires a better understanding of the mechanical and biochemical mechanisms that regulate normal and diseased tissue growth and development. The present invention discloses an engineered system that allows the culture and mechanical/biochemical testing of small-scale rodent tissues. This miniature tissue culture system can be used to develop new tissue engineering methods and novel gene therapy solutions towards potential clinical treatments.

Description of the Technology

The design of the Miniature Tissue Culture System (MTCS) is unique in that manipulations can be conducted for positioning and cannulating small scale tissues all in a sealed culture bath environment. Currently, the MTCS has been configured to perfuse the mitral and aortic valves while they sit in their natural position in the heart, where we have successfully cultured the mitral valve of 10-day old mouse hearts for four days. However, other small-scale rodent tissues could also be cultured under perfusion in the MTCS; including: the whole heart, arteries, veins, kidneys, stomach, and intestines. The MTCS can also be used to study Gene Therapy techniques where it has already been successfully used to induce adenovirus-mediated gene transfer into the cultured valve.

Applications

- To culture rodent tissues under perfusion allowing mechanical and biochemical testing of tissues
- To study Gene Therapy methods by inducing adenovirus-mediated gene transfer into the cultured tissues
- To study the genetic (signaling pathways) and epigenetic (shear flow) factors involved in developing rodent tissues.
- To culture rodent heart valves, i.e. the mitral and the aortic valves, while sitting in their natural position in the heart.

Patent Status

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Compound Human α -synuclein Transgenic Mouse Model of the Parkinson's Disease Phenotype (*Richfield, EOSHI 06-52*) *Research Tools/Mouse Models/CNS*

Background

A role for both the wild-type and mutated forms of α -synuclein in humans with Parkinson's disease has been implicated. It is not yet known if both forms have the same mechanism or differ. Nor is it known how either contributes to the disease. UMDNJ researches have created several lines of transgenic mice with Parkinson's disease phenotype that will allow for better understanding of the roles of these genes in contributing to Parkinson's disease. Testing of interventions to slow or halt the progression of the disease would be best tested in the compound transgenic mice.

Description of the Technology

A transgenic mouse model of the Parkinson's disease phenotype was originally created in the C57BL/6J line. One line contained the wild-type human α -synuclein gene under control of the rat tyrosine hydroxylase promoter. The other line contained a doubly-mutated form of human α -synuclein. The transgenes have been crossed into a line of C57BL/6J mice that are spontaneously deleted in the mouse α -synuclein gene. The major advantage of this cross is that the actions of the human α -synuclein gene will not be altered by the action of the endogenous mouse α -synuclein gene. The different lines have transgene specific consequences on the dopaminergic neurons of the substantia nigra pars compacta which decline in humans and are responsible for many of the adverse effects in the disease. These consequences include loss of locomotor activity with aging associated with loss of striatal levels of the neurotransmitter dopamine.

Applications

- To study mechanisms of cell dysfunction and death in regions of the brain vulnerable in Parkinson's disease.
- For testing of interventions to slow or halt the progressive features or to provide symptomatic therapy.

Patent Status

Provisional Application Filed 2006

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