



Office of Patents and Licensing VACCINES & INFECTIOUS DISEASES

Technology Contact Information :

Peter Golikov, MS, MBA

Director, Ventures and Licensing
University of Medicine and Dentistry of
New Jersey

335 George Street,

New Brunswick, NJ 08901

Direct Phone: **(732)-235-9355**

Office Phone: (732)-235-9350

Fax: (732)-235-9358

golikope@umdnj.edu



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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.

Contact Information

Peter Golikov, MS, MBA
Director, Ventures and Licensing
Office of Patents and Licensing



A 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.

Contact Information

Peter Golikov, MS, MBA
Director, Ventures and Licensing
Office of Patents and Licensing



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

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

Contact Information

Peter Golikov, MS, MBA
Director, Ventures and Licensing
Office of Patents and Licensing



Long Term Maintenance of Lymphocytes *in-vitro* (Dr. Joseph Dougherty, UMDNJ 93-43) Research Tool & 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

The procedure of the present invention 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. These adherent cells are positive for cell surface markers such as MHC class II, PECAM I (CD31), and E-selectin (ELAM-1, CD62E) and proteins such as laminin and fibronectin but are negative for CD45, CD14, muscle-specific actin and Factor VII-related antigen. The T cells maintained in the culture system of the present invention retain the ability to respond to mitogens and allogeneic cells and both CD4+ and CD8+ T cells could be maintained *in vitro* for up to three months. Furthermore, the T cells maintained this way could be used as targets in retroviral mediated gene transfer indicating that these cells could be used in gene therapy applications.

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, pharmacological, clinical and diagnostic applications

Patent Status

United States patent 5,688,915 granted on November 18, 1997

Contact Information

Peter Golikov, MS, MBA
Director, Ventures and Licensing
Office of Patents and Licensing



Method of Vaccineless Vaccination (*Hartmut M. Hanauske-Abel, NJMS 06-45*)
Vaccines

Background

Vaccinations are generally performed with protein or nucleic acid molecules isolated from, and representing strategic elements of, a pathogen of interest. This approach is rendered ineffective if the pathogen is able to undergo escape mutations and rapidly generates pathogenic yet immunologically distinct and non-crossreactive progeny. Such situations are encountered with several viruses, in particular HIV-1. Viruses, upon infection of a host cell, invariably suppress the genetically preprogrammed response of self-destruction ('apoptosis'). The anti-apoptotic activity of viruses, forces infected cells to stay alive and keep on functioning for the purpose of virion production. This activity also blinds the immune system of an infected individual since apoptotic cells are known to be effective enhancers of immunogenicity of molecules they contain.

Description of the Technology

UMDNJ researchers postulated that a drug that blocks this virally mediated apoptotic paralysis and thus reactivates apoptosis of infected cells, delivers the pathogen in an apoptosis-enhanced manner to the immune system of the host and thus, provides for vaccination without vaccination. In support of this concept, two drugs were used to induce apoptosis preferentially of freshly obtained human primary target cells (peripheral blood mononuclear cells, PBMCs) acutely infected with patient-derived HIV-1 isolates. The presence of HIV-1 in PBMC cultures increased susceptibility to drug-triggered apoptosis. Use of the medications of the present invention without interruption for up to three weeks reduced the number of infective virions produced to undetectable levels. The susceptibility to re-infection, as assessed by p24 levels, was markedly reduced, and after one week, p24 levels in reinfected, previously HIV-1 experienced cultures were less than 30% of those in controls.

Patent Status

Provisional Patent Application filed 2006

Contact Information

Peter Golikov, MS, MBA
Director, Ventures and Licensing
Office of Patents and Licensing



New Drug Combination for the Treatment of Viral Diseases (*Dr. Roger Strair, RWJ 94-41*) HIV

Background

Genetic heterogeneity is a major obstacle in the pharmacologic treatment of HIV infection. Current antiretroviral therapies such as AZT offer only limited benefits against HIV infection due to the emergence of resistant variants. However, the emergence of variants cannot completely explain certain phenomena such as the inability of viral isolates to replicate in vitro in tissue culture in the presence of AZT. By contrast, resistance to non-nucleoside inhibitors develops readily in both tissue culture and in patients. The resistance to non-nucleoside inhibitors arises, presumably, due to the selection of genetic variants because these inhibitors are not metabolized. Resistance to AZT develops over months as opposed to resistance to non-nucleoside reverse transcriptase inhibitors, which develops rapidly. These differences can be attributed a) to the inherent differences in the ability of individual cells in a cell population to uptake and metabolize drugs and also b) to pre-existing viral-encoded drug resistance mutations in the initial viral population prior to their exposure to antiretroviral drugs. These differences could allow the selective replication of viral variants sensitive to drugs in cells that do not readily uptake and metabolize antiretrovirals such as AZT. Thus, the metabolic factors involved in the metabolism of AZT represent potential opportunities to modulate the clinical effectiveness of this drug.

Description of the Invention

Previous studies have demonstrated that the emergence of HIV variants in the presence of Stavudine is a result of infection of cells refractory to the drug. In an effort to overcome the ineffectiveness of AZT, UMDNJ investigators have used a novel approach to modulate the effects of AZT. This approach involves manipulating the biochemical pools of phosphorylated thymidine. By co-administering a thymidine analog, which is a reverse transcriptase inhibitor, and an antimetabolite that is a thymidylate synthase inhibitor, the viral burden was reduced significantly. The use of thymidylate synthase inhibitor augments antiviral effect of the thymidine analog. Further, it was found that the antiviral effects of thymidine analog can be enhanced when administered with thymidylate synthase inhibitor and a folate antagonist.

Patent Status

US Patent granted on June 10, 2003. Patent No.: 6,576,622 B1.

Contact Information

Peter Golikov, MS, MBA
Director, Ventures and Licensing
Office of Patents and Licensing



HIV Antibodies & Vaccines (*Dr. Abraham Pinter, PHRI/UMDNJ*) HIV

Background

A major factor thwarting the development of a successful human immunodeficiency virus type 1 (HIV-1) vaccine is the development of resistance of the virus to neutralizing antibodies induced after infection or immunization. Sequence variability at major neutralizations sites contributes to this effect. Recent evidence argues that the major factor in this resistance is conformational shielding of susceptible epitopes. N-linked glycans located in various regions play a general role in epitope masking, and increasing evidence documents a dominant role for the V1/V2 domain in such masking. This potentially critical role of conformational masking in neutralization resistance poses a major conundrum for HIV vaccine development. The limited number of known neutralization targets that are insensitive to masking, such as those seen by broadly neutralizing monoclonal antibodies (MAbs) b12, 2G12, and 2F5, are poorly immunogenic, and are difficult to elicit. Thus it is important to identify additional immunogenic targets that can mediate potent neutralization and that are either reasonably well conserved or present in a limited number of variants suitable for formulation into a multivalent vaccine.

Description of the Technologies

The present series of technologies emerged from the laboratory of a prominent HIV researcher, Dr. Abraham Pinter from Public Health Research Institute (PHRI/UMDNJ) and relates HIV antibody and vaccine development. More specifically, novel expression vectors for expression of a fusion glycoprotein are provided that contains the N-terminal globular domain of a retroviral env surface protein linked to a selected glycopeptide. Truncation glycoproteins as well as insertion glycoproteins can be expressed using these vectors. Additionally, a synergistic combination of antibodies specific for HIV envelope glycoprotein gp120 is disclosed. One of the antibodies is specific for the V3 loop and the other is specific for the CD-4 binding site of gp120. A separate invention features a protein, which includes a gp120 V1/V2 domain of an HIV-1 strain. This protein displays an epitope, which is recognized by an antibody, which neutralizes at least one HIV-1 primary isolate with a ND₉₀ of less than 100 µg/mL. Additionally, the most recent invention discloses HIV-1 peptides, nucleic acids, and compositions, and uses thereof for production of HIV vaccines.

Patent Status

US Patents: 5,922,325; 5,643,756; 5,952,474; 6,815,201. Provisional Application: 60/830,044

Contact Information

Peter Golikov, MS, MBA
Director, Ventures and Licensing
Office of Patents and Licensing



Novel Class of Compounds to Control Chronic Hepatitis C Virus (*Dr. Neerja Kaushik-Basu, 06-49 UMDNJ*) Therapeutic

Background

Chronic Hepatitis C virus (HCV) infection is the leading cause of severe hepatitis that often progresses to cirrhosis, stasis, and hepatocellular carcinoma. Current therapies against HCV are limited in efficacy and have adverse side effects thus necessitating the development of new antiviral agents against this pathogen. The HCV RNA-dependent RNA polymerase (NS5B) is the key enzyme involved in the replication of the viral genome is unique to the virus and therefore represents an attractive target for drug development. **The present technology relates to a discovery of a novel class of compounds to control chronic Hepatitis C virus by inhibiting its replication.**

Description of the Technology

Researchers at UMDNJ have identified a class of compounds capable of inhibiting HCV NS5B. This has been shown utilizing a purified, functionally active recombinant NS5B in *in vitro* RNA dependent RNA polymerase (RdRp) activity of HCV NS5B on homopolymeric poly rA-U12 template primer. UMDNJ researchers have addressed the mechanism of inhibition by these compounds and identified that they compete with the template-primer in order to inhibit NS5B RdRp activity. In addition to inhibiting the HCV replicase, this family of compounds can potentially inhibit other RNA-dependent RNA/DNA polymerases of viral origin such as HIV-1RT, BVDV NS5B, Poliovirus RdRp, etc. Further studies are under way utilizing cell cultures and animal models.

Applications

- For the treatment of chronic Hepatitis C viral infection

Patent Status

United State provisional patent application filed

Contact Information

Peter Golikov, MS, MBA
Director, Ventures and Licensing
Office of Patents and Licensing



Non-Antibiotic Intervention of Chlamydial Infection (Dr. Huizhou Fan, 03-38 RWJ)
Infectious Diseases/Therapeutic

Background

Chlamydial infection is caused by Chlamydia trachomatis bacterium and is common among sexually active adolescents and young adults in the United States and in the developing world. As per U.S. Centers for Disease Control and Prevention estimates, there are 4 million new cases of Chlamydial infections each year. Chlamydial infection often results in abnormal discharge from female and male sexual organs and pain while urinating. If left untreated the infection may spread to other organs of the body causing pelvic inflammatory disease (PID) in women and epididymitis in men, inflamed rectum and inflammation of the eye. In women, PID is often asymptomatic and if left untreated, can lead to infertility. Current treatment methods include the use of antibiotics such as azithromycin or doxycycline or erythromycin or ofloxacin. The use of prescription antibiotics poses the risk of developing antibiotic resistance and disruption of normal microbial floras. Thus, there is a long felt medical need for alternative treatment strategies that overcome the aforementioned limitations. **The present technology represents a novel strategy to effectively prevent and eliminate C. trachomatis infection.**

Description of the Technology

UMDNJ researchers have discovered that the use of certain metalloprotease inhibitors prevent the production of infectious chlamydial progenies when used at both early and late stages of infections. In addition to preventing chlamydial growth, these compounds were found to enable host cells to resume chlamydia-blocked cell division.

Advantages

- Non-antibiotic treatment
- Normal microbial flora will not be destroyed

Applications

Prevention and treatment of chlamydial infection

Patent Status:

US Patent Application 11/572,546 filed 7/23/2004

Contact Information

Peter Golikov, MS, MBA

Director, Ventures and Licensing

Office of Patents and Licensing



Sepsis Prevention through Adenosine Receptor Modulation (*Hasko, RWJ 05-03*)
Therapeutic/Infectious Disease

Background

Sepsis is the single greatest cause of non-cardiac death in the hospital setting. Approximately 800,000 episodes of sepsis occur throughout the US leading to more than 200,000 deaths annually. Sepsis is a complex systemic syndrome that involves infection, inflammation, and ultimately multiorgan system failure. At present, there are limited therapeutic options for improving patient outcome in sepsis beyond, antibiotics, fluids, vasopressors, supportive intensive care, and occasionally low-dose corticosteroids.

Description of the Technology

The novel technology provides a new way to treat sepsis by modulating adenosine A2a receptor subtype by a novel small molecule antagonist, named ZM241385. Adenosine receptors play an important role in modulating the innate immune response. Adenosine is a potent endogenous anti-inflammatory and immunosuppressive molecule that is released from cells into the extra-cellular space at sites of inflammation and tissue injury. Once released, adenosine diffuses to the cell membrane of surrounding cells and binds specific cell-surface receptors. The four known adenosine receptors are G-protein coupled receptors. Each adenosine receptor has its unique signal transduction mechanism, ligand affinity, and tissue distribution.

Applications

- The technology provided a new therapeutic strategy to treat sepsis by modulating the Adenosine A2a receptor sub-type.
- The technology includes a novel small molecule Adenosine A2a receptor sub-type antagonist prototype.
- The technology provides a novel target to discover additional therapeutic agents for the treatment of sepsis.

Patent Status

International Application for Patent (PCT/US2006/003523) was filed on February 1, 2006.

Contact Information

Peter Golikov, MS, MBA
Director, Ventures and Licensing
Office of Patents and Licensing

