

Current treatments for pain, especially chronic pain, are only partially effective and can eventually involve procedures that are invasive or associated with unacceptable side effects. In vivo gene transfer could be used to directly modulate pain and provide a long-term pain control. This invention describes a method of using an adenovirus or an adeno-associated virus that are genetically engineered to deliver DNA encoded peptides or proteins to neurons involved in the transmission of pain. The invention provides for a novel means to treat chronic pain by administering a beta-endorphin-expressing recombinant adenovirus into the subarachnoid space. The recombinant virus infects the pia mater connective tissue cells and the infected cells express the fusion protein, wherein the fusion protein is cleaved and the neuroactive product is secreted into spinal cord parenchymal tissue in an amount effective to treat the chronic pain but not significantly affecting basal nociceptive responses. The invention demonstrates a gene transfer approach to treatment of chronic pain disorders or cancer pain, and may be generalized to spinal cord injury or neurodegenerative disorders.

O²-Arylated or O²-Glycosylated 1-Substituted Diazen-1-ium-1,2-diolates and O²-Substituted 1-[(2-Carboxylato)Pyrolidin-1-yl] Diazen-1-ium-1,2-diolates

JE Saavedra, LK Keefer, A Srinivasan, C Bogdan, WG Rice, X Ji, (NCI)
DHHS Reference No. E-093-96/3 filed 26 Sep 97 (U.S. Patent Application Serial No. 09/254,301 filed 03 Mar 99, based on Provisional U.S. Patent Applications No. 60/026,816 filed 27 Sep 96, No. 60/045,917 filed 07 May 97, and No. 60/051,696 filed 03 Jul 97)

Licensing Contact: Kai Chen; 301/496-7056 ext. 247; e-mail: kc169a@nih.gov

Diazeniumdiolates are compounds that contain an N₂O₂ functional group. These compounds are potentially useful as prodrugs 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. Derivatives of diazeniumdiolates have been produced that degrade under differing environmental conditions, allowing for selective delivery of nitric oxide in a manner dependent on environment. A new series of diazeniumdiolate

derivatives has been synthesized that are stable in neutral to acidic environments and generate nitric oxide in basic or nucleophilic environments. These derivatives are potentially suited to the delivery of nitric oxide to basic or nucleophilic compartments within the body. They may be useful for inactivating proteins to prevent detoxification of chemotherapeutic agents or disruption of proteins active in tumor formation, infection, or regulatory activities. The compounds are stable in an aqueous environment but can be activated by enzymatic action to release nitric oxide that is believed to be useful in treating fulminant liver failure, respiratory problems, impotence, and a variety of cardiovascular/hematologic disorders. The diazeniumdiolates have also been derivatized by their incorporation into polymers. These compounds may allow for site specific delivery of nitric oxide. Overall, these compounds appear to be applicable toward the wide variety of processes involving nitric oxide.

Immunologically Active Peptides From the HIV Envelope Protein Eliciting Both Antibody and T Cell Responses

William R. Kenealy, Stephen R. Petteway and Paul J. Durda
U.S. Patent No. 5,562,905 issued 08 Oct 96

Licensing Contact: Robert Benson; 301/496-7056 ext. 267; e-mail: rb20m@nih.gov

This invention is a series of chemically synthesized peptides of about 15 amino acids in length from the gp160 envelope protein of various isolates of HIV-1. Antibodies raised against the peptides block proliferation of HIV and block HIV-induced cell fusion in cell culture. The peptides are potential vaccines against HIV infection and monoclonal antibodies raised against the peptides are potentially useful as therapeutics. Foreign equivalent cases to USSN 07/148,692 (Berzofsky et al., PCT/US89/00712) are also available for licensing.

The NIH has many other patents and pending patent applications, most foreign filed, claiming various peptides from the HIV envelope protein that are T helper epitopes, CTL epitopes and neutralizing antibody epitopes discovered in the laboratory of Dr. Jay Berzofsky. Dr. Berzofsky has designed synthetic chimeric peptides (called "multideterminant" peptides) that combine a peptide containing several T helper epitopes which can activate many human HLA types (called a "multicenter" peptide, and claimed in USSN 08/455,685) with a peptide combining a CTL and neutralizing B cell

epitope (called a "p18" peptide, and claimed in USSN 07/847,311 and U.S. patents 5,820,865 and 5,562,905). These multideterminant peptides contain only epitopes that lead to protection without containing epitopes that are detrimental to protection. Two of the multicenter chimeric peptides are in clinical trials. Multideterminant peptides are claimed in USSN 08/060,988 and 08/407,252.

Computational Analysis of Nucleic Acid Information Defines Binding Sites

Thomas D. Schneider (NCI), Peter K. Rogan

Serial No. 08/494,115 filed 23 Jun 95; U.S. Patent 5,867,402 issued 02 Feb 99

Licensing Contact: John Fahner-Vihtelic, 301/496-7735, ext. 270; e-mail: jf36z@nih.gov

Current approaches to determine whether a nucleotide change is a benign polymorphism or is associated with a genetic disease rely on sequence comparisons of a substantial number of individuals. This invention embodies a computational method that is able to predict whether a nucleotide change will have a deleterious effect. The claims of this invention relate to a computer program which has the novel feature in that it is designed to calculate the relative importance of a given nucleotide change. This program is unique in that it is capable of predicting the effect that a given nucleotide change would have on a particular sequence such as a known binding site. The method has been successfully applied to predicting the effects of changes at human splice junctions. Further information is available at "<http://www.lecb.ncifcrf.gov/~toms/walker/index.html>".

Dated: May 26, 1999.

Jack Spiegel,

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

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BILLING CODE 4140-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing: Cyanovirin-based Topical Microbicides for Prevention of Sexual Transmission of HIV

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

ACTION: Notice.

SUMMARY: The U.S. National Institutes of Health seeks exclusive or non-exclusive licensee(s) for certain aspects of technology encompassed within the following U.S. (and corresponding international) patent and patent application: 5,843,882 issued December 1, 1998, entitled "Antiviral Proteins and Peptides", and Serial No. 08/969,378 filed November 13, 1997, entitled "Methods of Using Cyanovirins to Inhibit Viral Infectivity" (in accordance with 35 U.S.C. 207 and 37 CFR Part 404).

More specifically, licensee(s) is (are) sought to develop and commercialize microbicidal compositions, formulations, devices and/or methods directly incorporating the unique, HIV-inactivating protein, cyanovirin-N (CV-N), for topical use to prevent sexual transmission of HIV infection and disease.

ADDRESSES: Inquiries concerning this licensing opportunity should be directed to Dr. Carol Salata, Technology Licensing Specialist, Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852-3804; telephone: 301-496-7735 ext. 232; fax: 301-402-0220; e-mail: salatac@od.nih.gov. A signed Confidential Disclosure Agreement will be required to receive copies of the patent application.

SUPPLEMENTARY INFORMATION: The development of an effective anti-Hiv topical microbicide, especially a female-controlled, vaginal microbicide, has been deemed an urgent global priority by numerous international agencies, including the World Health Organization, the U.S. Department of Health and Human Services, the National Institute of Allergy and Infectious Diseases, and others.

Cyanovirin-N (CV-N) is a unique, 101 amino acid protein discovered,¹ by U.S. government scientists, as a constituent of a cultured cyanobacterium, *Nostoc ellipsosporum*. CV-N has subsequently been produced recombinantly in *E. coli*.³ Both the sequence¹ and the 3-D solution structure² of CV-N are unprecedented.

CV-N potently and irreversibly inactivates diverse primary strains of HIV-1, including M-tropic forms involved in sexual transmission of HIV, as well as T-tropic and dual-tropic forms; CV-N also blocks cell-to-cell transmission of HIV infection.¹ CV-N is directly virucidal, interacting in an unusual manner with the viral envelope, apparently binding with extremely high affinity to poorly immunogenic epitopes on gp120.^{1, 3}

CV-N was benign *in vivo* when tested in the rabbit vaginal toxicity/irritancy model, and was not cytotoxic *in vitro* against human immune cells and lactobacilli (unpublished). CV-N is readily soluble in aqueous media, is remarkably resistant to physicochemical degradation,¹ and is amendable to very large-scale production by a variety of genetic engineering approaches.

Selected References

1. Boyd, M.R., Gustafson, K.R., McMahon, J.B., Shoemaker, R.H., O'Keefe, B.R., Mori, T., Gulakowski, R.J., Wu, L., Rivera, M., Laurentot, C.M., Cardellina, J.H. II, Buckheit, R.W. Jr., Nara, P.L., Pannell, L.K., Sowder, R.C. II, Henderson, L.E.: Discovery of cyanovirin-N, a novel human immunodeficiency virus-inactivating protein that binds viral surface envelope glycoprotein gp120; potential applications to microbicide development. *Antimicrob. Agents Chemother.* 41: 1521-1530, 1997.
2. Bewley, C.A., Gustafson, K.R., Boyd, M.R., Covell, D.G., Bax, A., Clore, G.M., Gronenborn, A.M.: Solution structure of cyanovirin-N, a potent HIV-inactivating protein. *Nature Struct. Biol.* 5: 571-578, 1998.
3. Mori, T., Gustafson, K.R., Pannell, L.K., Shoemaker, R.H., Wu, L., McMahon, J.B., Boyd, M.R.: Recombinant production of cyanovirin-N, a potent HIV (human immunodeficiency virus)-inactivating protein derived from a cultured cyanobacterium. *Protein Expr. Purif.* 12: 151-158, 1998.
4. Esser, M.T., Mori, T., Mondor, I., Sattentau, Q., Dey, B., Berger, E.A., Boyd, M.R., Lifson, J.D.: Cyanovirin-N binds to gp120 to interfere with CD4-dependent HIV-1 virion binding, infectivity, and fusion, but does not affect the CD4 binding site on gp120 or soluble CD4 induced conformational changes in gp120. *J. Virol.* 73:4360-4371, 1999.

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Jack Spiegel,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

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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 contacting Girish C. Barua, Ph.D. at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852-3804; telephone: 301/496-7056 ext. 263; fax: 301/402-0220; e-mail: gb18t@nih.gov. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Modulation of N-Acetyl-Transferase To Improve Therapy and Prevent Cancer

Jerry M. Collins, Raymond W. Klecker, Aspandiar G. Katki (FDA)
DHHS Reference No. E-268-98/0 filed 16 Apr 99

This technology describes a method in which an inhibitor of an arylamine N-acetyl transferase (NAT), a member of a common enzyme family, is administered to a human to inhibit acetylation reactions resulting in production of cytotoxic or carcinogenic compounds in the treated individual. Nearly all drugs are metabolized in the human body by enzymes. Although metabolism generally lowers the toxicity of drugs, the opposite effect is often encountered with NAT. With NAT, the resulting metabolite is more toxic than the parent drug. Administering an inhibitor of NAT with such drugs is believed to result in decreased toxicity to the patient because of reduced exposure to the metabolite. Reduced exposure to the metabolite is believed to be beneficial to patients because the reduction in toxicity results in the maximization of the benefits of the parent drug. Accordingly, this method could be utilized in many therapeutic areas, since drugs which are metabolized by NAT are used in most medical disciplines, including heart disease, infectious diseases, and oncology. The technology also describes the acetylation capacity of NAT's link to human tumors. The acetylation capacity can be reduced by an enzyme inhibitor which may lead to a decrease in human cancer. This concept identifies NAT as a novel target, to expand and improve a general strategy which is currently-emerging, known as "chemoprevention". Finally, the technology describes specific inhibitors