

APCs also enhances the interaction of HAVCR1 with HAV.

Aspects of the technology are further described in Tami *et al.*, 2007. *J. Virol.*, in press.

**Applications:** Therapies that target the interaction of HAVCR1 with the ligand on APCs, such as small molecules or monoclonal antibodies, can control immune responses, the development of asthma, allergies and other atopic diseases, hepatitis A, kidney regeneration, and cancer.

**Development Status:** The technology is in early stages of development.

**Inventors:** Gerardo Kaplan (CBER/FDA), *et al.*

**Patent Status:** U.S. Provisional Application No. 60/865,631 filed 13 Nov 2006 (HHS Reference No. E-035-2005/0-US-01).

**Licensing Status:** Available for non-exclusive or exclusive licensing.

**Licensing Contact:** Cristina Thalhammer-Reyero, PhD, M.B.A.; 301/435-4507; [thalhamc@mail.nih.gov](mailto:thalhamc@mail.nih.gov).

**Collaborative Research Opportunity:** The Food and Drug Administration, Center of Biologics Research and Evaluation, Laboratory of Hepatitis and Related Emerging Agents, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize the hepatitis A virus cellular receptor as a potent activator of antigen presenting cells. Please contact Beatrice Droke, 301/872-7008 or [beatrice.droke@fda.hhs.gov](mailto:beatrice.droke@fda.hhs.gov), for more information.

### **Cyanovirins and Related Conjugates, Compositions, Nucleic Acids, Vectors, Host Cells, Methods of Production and Methods of Use for Microbicide Development**

**Description of Technology:** 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. The present invention provides antiviral proteins (collectively referred to as cyanovirins), conjugates thereof, DNA sequences encoding such agents, host cells containing such DNA sequences, antibodies directed to such agents, compositions comprising such agents, and methods of obtaining and using such agents for the production of microbicides.

Cyanovirin-N (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. 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. Further, cyanovirin-N (CV-N) and homologous proteins and peptides potently inhibit diverse isolates of influenza viruses A and B, the two major types of influenza virus that infect humans.

The described technology includes glycosylation-resistant mutants of CV-N, which code sequences to enable ultra large-scale recombinant production of functional cyanovirins in non-bacterial (yeast or insect) host cells or in transgenic animals or plants. Therefore, these glycosylation-resistant mutants may allow industry to produce CV-Ns on a large scale and make CV-Ns cheap enough for developing countries to benefit from this invention.

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 and is amenable to very large-scale production by a variety of genetic engineering approaches.

**Applications:** Development of microbicides against HIV and influenza.

**Development Status:** Preclinical data is available at this time.

**Inventors:** Michael Boyd (NCI), Robert Shoemaker (NCI), Barry O'Keefe (NCI), Toshiyuki Mori (NCI), Angela Gronenborn (NIDDK).

#### **Related Publications:**

1. B Giomarelli, R Provvedi, F Meacci, T Maggi, D Medaglini, G Pozzi, T Mori, JB McMahon, R Gardella, MR Boyd. The microbicide cyanovirin-N expressed on the surface of commensal bacterium *Streptococcus gordonii* captures HIV-1. *AIDS*. 2002 Jul 5;16(10):1351-1356.

2. CC Tsai, P Emau, Y Jiang, MB Agy, RJ Shattock, A Schmidt, WR Morton, KR Gustafson, MR Boyd. Cyanovirin-N inhibits AIDS virus infections in vaginal transmission models. *AIDS Res Hum Retroviruses*. 2004 Jan;20(1):11-18.

#### **Patent Status:**

1. Patent Cooperation Treaty Serial No. PCT/US00/06247 filed 10 Mar 2000; National Stage Filing in United States, Japan, Australia, Europe, Germany, France, China, United Kingdom, and Belgium (HHS Reference No. E-074-1999/2).

2. Patent Cooperation Treaty Serial No. PCT/US99/18975 filed 19 Aug 1999; National Stage Filing in United States, Japan, Australia, Europe, Germany, France, China, United Kingdom, and Belgium (HHS Reference No. E-117-1995/3).

**Licensing Status:** Available for licensing and commercial development.

**Licensing Contact:** Sally Hu, PhD; 301/435-5606; [HuS@mail.nih.gov](mailto:HuS@mail.nih.gov).

**Collaborative Research Opportunity:** The National Cancer Institute's Molecular Targets Development Program is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize microbicides for HIV and influenza. Please contact John D. Hewes at (301) 435-3121 or [hewesj@mail.nih.gov](mailto:hewesj@mail.nih.gov) for more information.

Dated: March 16, 2007.

**Steven M. Ferguson,**

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

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**BILLING CODE 4140-01-P**

## **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

### **National Institutes of Health**

#### **Government-Owned Inventions; Availability for Licensing**

**AGENCY:** National Institutes of Health, Public Health Service, HHS.

**ACTION:** Notice.

**SUMMARY:** The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

**ADDRESSES:** Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852-3804; *telephone:* 301/496-7057; *fax:* 301/402-0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

### Enhanced Function of Gene Modified T-Cells: Identification of T-Cell Receptors (TCR) with Altered Amino Acid Sequence

*Description of Technology:* A major limitation of the current chemotherapy-based therapeutics is the cytotoxic side-effects associated with them. Thus there is a dire need to develop new therapeutic strategies with fewer side-effects. Immunotherapy has taken a lead among the new cancer therapeutic approaches. Adoptive immunotherapy is one of the most promising new therapeutic approaches that enhance the innate immunity of an individual to fight against a certain disease.

T cell receptors (TCR) are the proteins responsible for the T cell's ability to recognize infected or transformed cells. TCR consists of two domains, one variable domain that recognizes the antigen and one constant region that helps the TCR anchor to the membrane and transmit the recognition signal by interacting with other proteins.

This invention is directed to substitutions in gene sequences that code for T cell receptors, specifically the inventors found that one to two amino acid substitutions in the TCRs that recognize 1G4 XY-ESO-1 and MART-1 resulted in a marked increase of these modified TCRs to recognize tumor cell targets. These mutated sequences are currently being evaluated as candidates for clinical development. The inventors also consider the invention as providing a "general paradigm" that will allow the generation of TCR directed against a variety of antigens that can enhance the function of gene modified T cells.

#### *Applications:*

1. Improved ability of modified TCRs to recognize tumor cell targets.
2. High affinity TR can be generated that recognizes a variety of antigens that can be potentially used for the diagnosis and treatment of patients with a variety of conditions that include cancer, infectious diseases and autoimmunity.
3. Mutant high affinity TR can also be used to transduce T cells in order to generate cells reactive with tumor antigens as well as viral antigens.

*Development Status:* Pre-clinical work has been completed and clinical work is undergoing.

*Inventors:* Paul F. Robbins (NCI), Steven A. Rosenberg (NCI), Richard A. Morgan (NCI), *et al.*

*Relevant Publication:* A manuscript relating to this invention is under preparation and will be available once accepted.

*Patent Status:* U.S. Provisional Application No. 60/847,447 filed 26 Sep 2006 (HHS Reference No. E-304-2006/0-US-01).

*Licensing Status:* This technology is available for licensing under an exclusive or non-exclusive patent license.

*Licensing Contact:* Michelle Booden, PhD; 301/451-7337; [boodenm@mail.nih.gov](mailto:boodenm@mail.nih.gov).

*Collaborative Research Opportunity:* The NIH Surgery Branch is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize adoptive immunotherapy. Please contact John D. Hewes, PhD at 301-435-3121 or [hewesj@mail.nih.gov](mailto:hewesj@mail.nih.gov) for more information.

### Novel Benzindole Based Compounds for HIV Therapy

*Description of Technology:* The HIV/AIDS epidemic continues despite efforts from scientists, drug companies, and non-profit organizations. Although the existing therapy, is effective in the treatment of many infected individuals in developed nations, the infected individual is not cured and therapy must be life-long. There are problems with drug toxicity, the development of resistant viral strains, and with the cost of therapy. New anti-viral agents are needed for a more effective, and a more cost-effective, treatment of HIV.

The invention describes compounds based on a benzindole moiety, which alkylates DNA. The compounds comprise a benzindole moiety, a bifunctional linker, and a fatty acid residue or dendrimer residue comprising at least one fatty acid. Several benzindole derivatives are synthesized. The compounds bind to the minor groove of DNA and can be useful in the inhibition of gene expression. The advantage of the compounds is that they remain inactive until conformational change induced by DNA binding makes them active. The fatty acid moiety immobilizes them on the cytoplasmic side of the plasma membrane. These anchored compounds are specifically designed to inhibit retroviral DNA before it translocates to the host nucleus and integrates with the host genome.

#### *Applications and Modality:*

1. Novel benzindole-based compounds for HIV therapy.
2. Compounds are specifically designed to inhibit retroviral DNA before it can integrate with the host genome.
3. Additionally, compounds might have potential anti-cancer activities.

#### *Market:*

1. More than 45 million people are living with HIV/AIDS worldwide.

2. More than 3 million estimated deaths due to HIV/AIDS occurred worldwide in 2003.

3. HIV/AIDS epidemic has caused more than 30 million deaths.

*Development Status:* The technology is currently in the pre-clinical stage of development.

*Inventors:* Christopher J. Michejda (NCI), Stephen H. Hughes (NCI), *et al.*

*Relevant Publication:* A manuscript directly related to the above technology will be available as soon as it is accepted for publication.

*Patent Status:* U.S. Provisional Application No. 60/850,437 filed 10 Oct 2006 (HHS Reference No. E-126-2006/0-US-01).

*Licensing Availability:* Available for exclusive and non-exclusive licensing.

*Licensing Contact:* Adaku Nwachukwu, J.D.; 301/435-5560; [madua@mail.nih.gov](mailto:madua@mail.nih.gov)

*Collaborative Research Opportunity:* The National Cancer Institute's Structural Biophysics Laboratory is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize novel benzindole based compounds for HIV therapy. Please contact John D. Hewes, PhD at 301-435-3121 or [hewesj@mail.nih.gov](mailto:hewesj@mail.nih.gov) for more information.

### Cloning and Characterization of an Avian Adeno-Associated Virus and Uses Thereof

*Description of Technology:* Currently, adeno-associated virus (AAV) represents the gene therapy vehicle of choice because it has many advantages over current strategies for therapeutic gene insertion. AAV is less pathogenic than other virus types; stably integrates into dividing and non-dividing cells; integrates at a consistent site in the host genome; and shows good specificity towards various cell types for targeted gene delivery.

To date, 11 AAV isolates have been isolated and characterized. New serotypes derived from non-human animal species have added to the specificity and repertoire of current AAV gene therapy techniques by avoiding the immunologic complications associated with human isolates.

This invention describes vectors derived from an avian AAV. These vectors have innate properties related to their origin that may confer them with a unique cellular specificity in targeted human gene therapy and a unique immunologic profile that would avoid neutralization by pre-existing antibodies. Therefore, vectors derived

from this avian AAV are likely to find novel applications for gene therapy in humans. Furthermore because of their species of origin, this vector would also be useful in the engineering of avian cells.

*Inventors:* Ioannis Bossis and John A. Chiorini (NIDCR).

*Publication:* I Bossis, JA Chiorini. Cloning of an avian adeno-associated virus (AAAV) and generation of recombinant AAAV particles. *J Virol.* 2003 Jun;77(12):6799–6810.

*Patent Status:* U.S. Patent Application No. 10/557,662 filed 21 Dec 2006 (HHS Reference No. E-105-2003/0-US-03).

*Licensing Status:* Available for non-exclusive or exclusive licensing.

*Licensing Contact:* Jesse S. Kindra, J.D.; 301/435-5559; [kindraj@mail.nih.gov](mailto:kindraj@mail.nih.gov)

*Collaborative Research Opportunity:* The National Institute of Dental and Craniofacial Research, Laboratory of Dr. John Chiorini, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize gene therapy methods using AAV vectors. Please contact David W. Bradley, PhD at [bradleyda@nidcr.nih.gov](mailto:bradleyda@nidcr.nih.gov) for more information.

#### Serotonin-Deficient Knock-Out Mouse

*Description of Technology:* Serotonin is an important modulator of many developmental, behavioral, and physiological processes, and it has been implicated in depression, anxiety, schizophrenia, obsessive compulsive disorders, and substance abuse. Serotonin's pharmacology is extremely complex and it is mediated by seven of serotonin receptor subtypes and it is present in several tissues. Although it has been a subject of a number of studies, its role has been difficult to ascertain. To investigate the role of serotonin in these disorders, the murine gene was disrupted by homologous recombination. Results indicate that serotonin binding sites were absent in different brain regions (brain stem, frontal cortex, hippocampus, and striatum), and its concentrations were reduced by 60–80%. These mice represent a powerful tool for the investigation of behavioral and neuropsychiatric disorders, and development of drug treatments for these disorders.

*Applications:* A model to study serotonin's role in behavioral and neuropsychiatric disorders.

#### Market:

1. Serotonin inhibitors are most widely used treatment in

neuropsychological disorders. Examples include Zoloft, Paxil, and Prozac.

2. Depression effects approximately 18.8 million U.S. citizens and over 121 million people worldwide.

3. Antidepressant market was worth \$16.2 billion in 2005, and it has annual growth of 2% year on year.

4. Anxiety disorders affect 40 million (18.1%) of the adult U.S. population.

5. Global anxiety disorder market was \$4.5 billion in 2006.

*Inventors:* Dennis L. Murphy (NIMH) *et al.*

#### Publications:

1. RF Ren-Patterson, LW Cochran, A Holmes, S Sherrill, SJ Huang, T Tolliver, K-P Lesch. Loss of brain-derived neurotrophic factor gene allele exacerbates brain monoamine deficiencies and increases stress abnormalities of serotonin transporter knockout mice. *J Neurosci Res.* 2005 Mar 15;79(6):756–771.

2. DL Murphy, A Lerner, G Rudnick, K-P Lesch. Serotonin transporter: gene, genetic disorders, and pharmacogenetics. *Mol Interv.* 2004 April;4(2):109–123.

3. RF Ren-Patterson, D-K Kim, X Zheng, S Sherrill, S-J Huang, T Tolliver, DL Murphy. Serotonergic-like progenitor cells propagated from neural stem cells in vitro: survival with SERT protein expression following implantation into brains of mice lacking SERT. *FASEB J.* 2005 Sep;19(11):1537–1539.

4. Q Li, A Holmes, L Ma, LD Van de Kar, F Garcia, DL Murphy. Medical hypothalamic 5-hydroxytryptamine (5HT)1A receptors regulate neuroendocrine responses to stress and exploratory locomotor activity application of recombinant adenovirus containing 5-HT1A sequences. *J Neurosci.* 2004 Dec 1;24(48):10868–10877.

5. F Kilic, DL Murphy, G Rudnick. A human serotonin transporter mutation causes constitutive activation of transport activity. *Mol Pharmacol.* 2003 Aug;64(2):440–446.

6. DL Murphy, GR Uhl, A Holmes, R Ren-Patterson, FS Hall, I Sora, S Detera-Wadleigh, K-P Lesch. Experimental gene interaction studies with SERT mutant mice as models for human polygenic and epistatic traits and disorders. *Genes Brain Behav.* 2003 Dec;2(6):350–364.

7. N Ozaki, D Goldman, WH Kaye, K Plotnicov, BD Greenberg, J Lappalainen, G Rudnick, DL Murphy. Serotonin transporter missense mutation associated with a complex neuropsychiatric phenotype. *Mol Psychiatry.* 2003 Nov;8(11):933–936.

*Patent Status:* HHS Reference No. B-019-1999/0—Research Tool.

*Licensing Status:* This technology is available as a research tool under a Biological Materials License.

*Licensing Contact:* Jennifer Wong; 301/435-4633; [wongje@mail.nih.gov](mailto:wongje@mail.nih.gov).

Dated: March 15, 2007.

**Steven M. Ferguson,**

*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

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#### Microdialysis Probe for Accessing Tissue *in-vivo*

*Description of Technology:* Available for licensing and commercial development is a microdialysis probe. This device permits *in-vivo* measurement of bioavailable substances (e.g., cytokines, growth factors, neuropeptides, inflammatory mediators, etc.) at picogram levels of concentration directly from soft tissue and organ systems. The probe may also serve as an *in-situ* drug delivery vehicle of micro doses of medication to specific anatomical sites by slow diffusion. It also permits measurement of efficacy of drug delivery, whether given orally, systemically or topically, at the local