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.

Phantasmidine, a Nicotinic Receptor Agonist for the Treatment of Addiction and Neurological Disorders

Description of Invention: The inventors have isolated and characterized an alkaloid, phantasmidine, from the skin of the Ecuadoran poison frog *E. anthonyi.* Phantasmidine is selective for β4-containing receptor subtypes, unlike many nicotinic receptor agonists currently in development, which target β2-containing receptor subtypes. This selectivity makes phantasmidine a unique pharmacological probe, as well as a promising lead compound for the development of selective therapeutics targeting β4-containing receptor subtypes, which appear to play any important role in nicotine addiction and other substance dependencies.

Nicotinic acetylcholine receptors (nAChRs) are broadly distributed in both the peripheral and central nervous systems; activation of brain nAChRs results in enhanced release of various key neurotransmitters. Dysfunction of these receptors is associated with a variety of neurological diseases, including nicotine addiction. Nicotinic agonists, which enhance action at nicotinic acetylcholine receptors, have been shown to possess potential clinical utility in many of these diseases, although development is hindered by the existence of a large number of nAChR subtypes with highly variable properties.

Alkaloids, such as epibatidine found in skin from the frog species *E. tricolor,* have been shown to activate nicotinic acetylcholine receptors. However, while epibatidine has been shown to be a powerful analgesic, it is also extremely toxic, so research has focused on the identification and development of less toxic analogs.

Applications

- Development of therapies for the treatment of addiction, including nicotine and alcohol addictions.
- Development of therapies for neurological diseases such as Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), and schizophrenia.
- Development of selective pharmacological probes for bioimaging, binding assays, and functional assays of nicotinic receptors.

Inventors: Richard W. Fitch *et al.* (NIDDK)

Related Publication: R Fitch *et al.* Phantasmidine: An epibatidine congener from the Ecuadorian poison frog *Epipedobates anthonyi.* J Nat Prod. 2010 Mar 26;73(3):331–337. [PubMed: 20337496]

Patent Status: U.S. Provisional Application No. 61/315,674 filed 19 March 2010 (HHS Reference No. E–125–2010/0–US–01).

Licensing Status: Available for licensing.

Licensing Contact: Tara Kirby, PhD; 301–435–4426; *tarak@mail.nih.gov.*

Transplant and Autoimmune Therapy Using T-Cells Expressing Programmed Death Ligand-1 (PD–L1)

Description of Invention: Transplant complications (graft rejection and graft-versus-host disease) and autoimmune diseases are primarily caused by T cell immune responses against normal host tissue or transplanted tissues. These disorders can lead to serious complications and may be chronic, debilitating, and fatal. Current treatment for these disorders is oftentimes not effective, and is typically associated with significant side effects, including global immune suppression, which increases the rate of infection and cancer. Hence, there is a need for new technologies to more specifically suppress the immune system for treatment of these diseases.

Programmed death (PD) ligand 1 (PD–L1) is an immune molecule present on regulatory T cells (Tregs), other suppressor cell populations, and tumor cells; the function of PD–L1 is to suppress the function of pathogenic T cells that express the PD1 receptor. Therefore, it has been hypothesized that the transfer of T cells that are enriched for PD–L1 expression might represent an effective method to suppress autoimmunity or transplant complications. Adoptive T cell therapy using Tregs is one such approach; however, this approach is limited due to the relative rarity of Tregs and their tendency to possess differentiation plasticity towards pathogenic T cell subsets such as the Th17 subset. Ex vivo co-stimulated and expanded effector T cells can be generated in sufficient numbers for cell therapy; however, such cells are not enriched for PD–L1 expression.

The current technology overcomes these limitations through transduction of co-stimulated T cells with a lentiviral expression vector that dictates T cell expression of PD–L1. In this method, the co-stimulated T cells acquire the immunosuppressant characteristics of Treg cells. The PD–L1 gene expression construct co-expresses a cell surface molecule (*i.e.,* CD19 or CD34) that allows enrichment of the gene-modified T cells to high purity. Also the construct co-expresses another gene, TMPK, which acts as a safety cell fate switch because the TMPK can specifically activate the cytotoxic prodrug, AZT. By incorporation of this TMPK/AZT cell fate safety switch, the current technology will allow for PD–L1 therapeutic delivery, with subsequent elimination of the therapeutic cells in the event of toxicity.

Applications: Co-stimulated T cells expressing the PD–L1, CD19–TMPK construct can be adoptively transferred into patients to: (1) Treat autoimmune diseases; (2) prevent graft-versus-host disease (GVHD), which remains the primary lethal complication after hematopoietic cell transplantation (HCT); and (3) prevent solid organ or HCT transplant rejection.

Advantages

(1) Relative to other proposed cell therapies such as Treg therapy, co-stimulated T cells expressing the gene construct can be manufactured in clinically relevant numbers, possess a defined mechanism of action, and can be specifically modulated (eliminated) in vivo.

(2) The proposed immuno-gene therapy would prove advantageous to current immune suppressive therapies, which cause many side effects.

Market

(1) Many diseases have been identified to represent autoimmune disorders, including but not limited to: inflammatory bowel disease (IBD; including Crohn's disease); multiple sclerosis (MS); systemic lupus erythematosis (SLE); rheumatoid arthritis; and immune-mediated (type-1) diabetes mellitus. Approximately 1 in every 31 people in the U.S. suffers from an autoimmune disease; women suffer disproportionately from autoimmune diseases as they represent about 75% of cases.

(2) Graft rejection can occur in the setting of solid organ transplantation (for example, pancreatic, renal, cardiac, and liver transplantation) and also occurs after hematopoietic stem cell or bone marrow transplantation (including matched sibling, unrelated donor, and cord blood transplantation). More than 19,000 transplants are performed each year in the United States and the prevalence of graft rejection is considerable in these transplant recipients. In addition to graft rejection, graft-versus-host disease (GVHD) represents a significant transplant complication. Acute GVHD can occur in all types of hematopoietic stem cell or bone marrow transplantation (matched related, unrelated, or cord blood) and ranges in incidence from 30–80%. Chronic disease can also occur in approximately 54–70% of hematopoietic stem cell transplant recipients.

Development Status: Early-stage development.

Inventors: Daniel H. Fowler and Shoba Amarnath (NCI).

Publication: Amarnath S, Costanzo CM, Mariotti J, Ullman JL, Telford WG, Kapoor V, Riley JL, Levine BL, June CH, Fong T, Warner NL, Fowler DH. Regulatory T cells and human myeloid dendritic cells promote tolerance via programmed death ligand-1. PLoS Biol. 2010 Feb 2;8(2):e1000302. [PubMed: 20126379].

Patent Status: U.S. Patent Application No. 61/261,081 filed 13 Nov 2009 (HHS Reference No. E–022–2010/0–US–01).

Related Technologies: HHS Reference No. E–058–2006.

Licensing Status: Available for licensing.

Licensing Contact: Surekha Vathyam, PhD; 301–435–4076; *Surekha.Vathyam@nih.gov.*

Collaborative Research Opportunity: The Center for Cancer Research, Experimental Transplantation and Immunology Branch, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize this technology. Please contact John D. Hewes, PhD at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

A New "Destination" for Protein Expression: A Lentiviral Gateway® Destination Vector for High-Level Protein Expression (pDEST–673)

Description of Invention: A laboratory at the Science Applications International Corporation in Frederick, MD (SAIC–Frederick) has developed a lentiviral vector, pDEST–673, for high protein expression yields in cells. The pDEST–673 vector combines three features that make it optimal for protein expression in lentiviruses: the pFUGW backbone, a Gateway® vector conversion cassette, and a neomycin antibiotic resistance marker. The pFUGW portion contains a highly potent polypurine tract (PPT) that allows for the production of higher viral titers within transfected cells and a woodchuck regulatory element (WRE) to enhance protein expression. The addition of the Gateway® conversion cassette converts the vector into a Destination vector and the neomycin resistance marker allows for researchers to select for stable transfectants using antibiotic selection (a feature not possessed by many lentiviral vectors). This lentiviral Destination vector should be useful for researchers desiring to utilize neomycin resistance to select for proteins expressed in cells stably transfected with lentiviruses.

Applications

- Research tool for high quantity production of a protein(s) of interest for studying the role of the protein(s) in a variety of biological processes, including pathologies such as cancers, infectious diseases, autoimmune diseases, and many other disorders.
- Research tool for selecting stable lentiviral transfectants following the insertion of the vector into tumor cells.
- Potential tool for enhancing production of proteins that are normally difficult to express in other types of bacterial, insect, or mammalian expression systems.

Advantages

- *The pFUGW backbone provides the pDEST–673 vector with optimal protein expression properties:* The polypurine tract (PPT) region in the vector allows for efficient viral transcription leading to increased lentiviral production in cells. The woodchuck regulatory element acts as a posttranscriptional enhancer to promote the conversion of more mRNA transcripts into protein to yield high-levels of the protein of interest. These elements are not found in most commercially available lentiviral vectors.
- *The incorporation of the neomycin resistance marker facilitates selection of the transfectants of interest:* Many laboratories rely on neomycin selection as a key selectable marker in their protein expression experiments. Few commercially available lentiviral vectors contain a neomycin resistance marker.

Inventors: Dominic Esposito (SAIC).

Selected Publications

1. A Ventura, *et al.* Cre-lox-regulated conditional RNA interference from transgenes. Proc. Natl. Acad. Sci. USA. 2004 Jul 13;101(28):10380–10385. [PubMed: 15240889].

2. C Lois, *et al.* Germline transmission and tissue-specific expression of transgenes delivered by lentiviral vectors. Science 2002 Feb 1;295(5556):868–872. [PubMed: 11786607].

Patent Status: HHS Reference No. E–119–2009/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Status: Available for licensing under a Biological Materials License Agreement.

Licensing Contact: Samuel E. Bish, PhD; 301–435–5282; *bishse@mail.nih.gov.*

A Hand Held Portable Device Based on Light Emitting Diodes (LEDs) as a Light Source for Use in the Detection of Counterfeit Pharmaceutical Drugs and Packaging

Purpose: The FDA is seeking a device company to commercialize its patent pending hand held portable device for the detection of counterfeited pharmaceuticals. The device will be based on the technology described below. The invention was further described and claimed in provisional patent application 61/165,395 filed March 31, 2009. The FDA scientists have built highly reliable prototypes of two different models of the device and demonstrated the validity of the device for multiple applications.

Description of Technology: A hand held portable device was designed and developed for use in the detection of counterfeit pharmaceutical products and packaging. The light source of the device emits different wavelengths of light onto a sample. The device incorporates the use of single wavelength light emitting diodes (LEDs) which generate intense single wavelengths of light. Two models of the device have been developed and

manufactured. The first model incorporates only LEDs at specific wavelengths and the second model incorporates a camera and display along with the LEDs at specific wavelengths. The different LED wavelengths of light interact with the sample by either being absorbed, reflected or by generating an apparent color change in the sample. The absorption, reflection or apparent color change by the sample may be observed using different colored goggles (yellow, orange, red). The fluorescence profiles of suspect pills can be compared with the authentic article to determine legitimacy. The device can be used for field examination of suspect counterfeit pharmaceutical products, packaging and diverted pharmaceutical products. Due to its size, and the simplicity in design and use, the hand held portable LED light source can be used by health safety officials (e.g. FDA investigators), by law enforcement authorities, or by the pharmaceutical companies themselves, to rapidly screen samples for suspect counterfeit products improving the safety of that the U.S. drug distribution chain.

Applications

- Testing for authenticity of pharmaceutical products.
- Combating the ever growing problem of counterfeiting in pharmaceutical products to protect public safety.
- Traditional law enforcement activities.

Advantages: Current methods of detecting counterfeit pharmaceuticals include vibrational spectroscopy, x-ray diffraction, gas chromatography, liquid chromatography, and mass spectrometry. These methods although often effective, require expensive and bulky instrumentation, and are generally performed in a laboratory by highly trained operators. The LED devices based on the subject technology thus offer the following advantages:

- Small size, light and portable.
- Tests can be performed at desired location outside of lab setting.
- Simple to use and does not require special technical skills.
- Low cost and simple to manufacture.
- Reliable and provides reproducible results.
- Image capture and storage capabilities.

Development Status: Fully developed and ready for manufacturing.

Market: The volume of counterfeit pharmaceuticals entering the United States and other countries continues to increase. Counterfeit pharmaceuticals are illegally imported and are commonly available over the Internet. It is often difficult to determine the authenticity of a pharmaceutical, since the genuine and counterfeit products often have nearly identical appearance and markings (shape, color, size, packing, labeling *etc.*), even when viewed by professionals. Detection of counterfeit pharmaceuticals is of extreme importance since the efficacy of a counterfeit product is often lower than the actual product. In addition, the counterfeit product may contain toxic components, and result in side effects which are not associated with the authentic product. Such counterfeit products also result in monetary loss to pharmaceutical companies and retailers. It is for these reasons, *i.e.* health safety and economic loss, that the commercial potential of devices that detect such counterfeit products is large. Due to the advantages offered by the subject invention as outlined above, it is predicted that both models of subject device will enjoy commercial success. The ease of use allows for examination of products anywhere an investigator or inspector can travel and gives a preliminary result that would allow action to be taken. The device has the potential to be expanded to uses related to product tampering, counterterrorism and other traditional law enforcement applications.

Inventors: Nicola Ranieri (FDA) *et al.*

Patent Status

- U.S. Provisional Application No. 61/165,395 filed 31 Mar 2009, entitled "Device and Method for Detection of Counterfeit Pharmaceuticals" (HHS Reference No. E–206–2008/0–US–01).
- PCT Application No. PCT/US2010/029502 filed 31 Mar 2010 (HHS Reference No. E–206–2008/0–PCT–03).

Licensing Status: Available for licensing.

Licensing Contacts

- Uri Reichman, PhD, MBA; 301–435–4616; *UR7a@nih.gov.*
- Michael Shmilovich, Esq.; 301–435–5019; *shmilovm@mail.nih.gov.*

Methods for Treatment and Diagnosis of Psychiatric Disorders

Description of Invention: Current drugs used to treat schizophrenia block dopamine receptors. These drugs can effectively suppress the "positive" symptoms of schizophrenia but have little impact on the debilitating or "negative" symptoms of the disease which include social withdrawal, emotional unresponsiveness, difficulty with attention and memory, and apathy. There is thus a therapeutic need for improved antipsychotics that can improve both positive and negative symptoms. This technology describes novel interactions between neuregulins (NRGs), ErbB receptors, and dopamine signaling pathways that may influence the expression of schizophrenia. Researchers at the NIH demonstrated that NRGs reverse long term potentiation (LTP) when given shortly after LTP is established without affecting basal transmission. Blockade of ErbB receptors with antagonists prevented depotentiation by NRG, and NRG showed no effect in an ErbB–4 knockout mouse model. Thus NRG regulation of LTP occurs through the ErbB–4 receptor. Data also showed that dopamine antagonists block the effects of NRGs on LTP. These findings could be useful in the development of antipsychotic drugs that block NRG actions, and in doing so, provide better therapies for schizophrenia.

This technology describes methods of treating schizophrenia with an antagonist that blocks neuregulin-1 activation of the ErbB–4 receptor signaling pathway, methods of identifying schizophrenia in affected patients, as well as methods of identifying modulators of ErbB–4 receptor signaling. This technology may also be applicable for treating or preventing other psychiatric disorders such as bipolar disorder, attention deficit disorder (ADD), and autism.

Applications

- Method of diagnosis and treatment for schizophrenia, bipolar disease, ADD and autism.
- Methods of finding modulators of ErbB–4 receptor signaling.

Market

- The U.S. schizophrenia market averages 10 billion dollars a year.
- Schizophrenia affects approximately 1% of the population.

Inventors: Andres Buonanno (NICHD).

Publications

1. Kwon OB, Longart M, Vullhorst D, Hoffman DA, Buonanno A. Neuregulin-1 reverses long-term potentiation at CA1 hippocampal synapses. J Neurosci. 2005 Oct 12;25(41):9378–9383. [PubMed: 16221846].

2. Kwon OB, Paredes D, Gonzalez CM, Neddens J, Hernandez L, Vullhorst D, Buonanno A. Neuregulin-1 regulates LTP at CA1 hippocampal synapses through activation of dopamine D4 receptors. Proc Natl Acad Sci USA. 2008 Oct 7;105(40):15587–15592. [PubMed: 18832154].

3. Vullhorst D, Neddens J, Karavanova I, Tricoire L, Petralia RS, McBain CJ, Buonanno A. Selective expression of

ErbB4 in interneurons, but not pyramidal cells, of the rodent hippocampus. 2009 J Neurosci. Sep 30;29(39):12255–12264. [PubMed: 19793984].

4. Buonanno, A. The neuregulin signaling pathway and schizophrenia: From genes to synapses and neural circuits. Brain Res Bull. 2010 Aug 3; Epub ahead of print. [PubMed: 20688137].

Patent Status

- U.S. Provisional Application No. 60/837,449 filed 11 Aug 2006 (HHS Reference No. E–304–2005/0–US–01).
- International Application No. PCT/US07/75724 filed 10 Aug 2007, which published as WO 2008/019394 on 14 Feb 2008 (HHS Reference No. E–304–2005/0–PCT–02).
- U.S. Patent Application No. 12/377,025 filed 10 Feb 2009 (HHS Reference No. E–304–2005/0–US–03).

Licensing Status: Available for licensing.

Licensing Contact: Jeffrey Clark Klein, PhD; 301–594–4697; *kleinjc@mail.nih.gov.*

Collaborative Research Opportunity: The National Institutes of Child Health and Human Development, Section on Molecular Neurobiology, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize this technology. Please contact John D. Hewes, PhD at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

Dated: September 20, 2010.

Richard U. Rodriguez,

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

[FR Doc. 2010–23977 Filed 9–23–10; 8:45 am]

BILLING CODE 4140–01–P

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Use of Adenosine Agonists To Prevent Arterial Vascular Calcification Disorder

Description of Invention: Scientists at the National Human Genome Research Institute (NHGRI) and the National Heart Lung and Blood Institute (NHLBI) at the National Institutes of Health (NIH) have discovered a genetic defect in the Ecto-5'-nucleotidase (*NT5E*) gene which results in Cluster of Differentiation 73 (CD73) deficiency that leads to a decrease in adenosine, and ultimately, an increase in vascular calcification. *NT5E* encodes CD73, an enzyme that converts adenosine monophosphate (AMP) to adenosine in the extracellular region of the vascular endothelium. Normally, extracellular adenosine binds to one of the several receptors on the surface decreasing the production of cyclic AMP (cAMP) resulting in an inhibition of vascular calcification.

The discovery of this genetic mutation leading to a decrease in adenosine provides a method of treating or preventing the disorder by using adenosine receptor agonists as therapeutic agents. Adenosine receptor agonists can be used to treat or prevent disorders associated with vascular and/or joint capsule calcification, including for example atherosclerosis, Monkeberg's medial sclerosis, CD74 deficiency, Ehlers Danlos syndrome (EDS), Marfan/Loewe Dietz syndrome, fibromuscular dysplasia, Kawasaki syndrome, pseudoxanthoma elasticum, and premature placental calcification.

Applications: Treatment for vascular calcification disorder by using adenosine receptor agonist agents.

Development Status: Early-stage.

Inventors: William A. Gahl (NHGRI), Thomas C. Markello (NHGRI), Shira G. Ziegler (NHGRI), Manfred Boehm (NHLBI), Cynthia Hillaire (NHLBI).

Publication: C St. Hilaire, et al. *NT5E* Mutations are Associated with Arterial Calcifications. New Engl J Med., Submitted 2010.

Patent Status: U.S. Provisional Application No. 61/319,336 filed 31 Mar 2010 (HHS Reference No. E–094–2010/0–US–01).

Licensing Status: Available for licensing.

Licensing Contact: Steve Standley, 301–435–4074, *sstand@od.nih.gov.*

Collaborative Research Opportunity: The NHGRI is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize adenosine receptor agonist compounds for therapeutic use including as a treatment of certain common as well as rare vascular calcification-related disorders (see above Description of Invention). Please contact NHGRI Technology Development Coordinator Claire T. Driscoll at *cdriscol@mail.nih.gov* for more information.

Small Molecule Neuropeptide S Receptor (NPSR) Antagonists for the Treatment of Addictive Disorders, Mood, Anxiety and Sleep Disorders

Description of Invention: The inventors, who work for the National Human Genome Research Institute (NHGRI) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) at the National Institutes of Health (NIH), have developed NPSR antagonists that hold the potential for being clinically useful treatments for alcohol and drug addiction. Neuropsychiatric disorders including, for example, mood, anxiety, eating, and sleep related disorders, as well as alcoholism and drug addiction, are major causes of mortality and morbidity. Patient relapse into drug seeking and use, after an interval of sobriety, is a key component of the addictive syndrome, with approximately two-thirds of patients relapsing within three months of initiating abstinence. Therefore, relapse prevention is a major treatment objective.

Neuropeptide S (NPS), an endogenous ligand for the Neuropeptide S receptor (NPSR) has recently been shown to play a key role in relapse-like behavior. In addition, because mood, anxiety, eating, and sleep related behaviors are often closely linked with the addictive process, and are also affected by the NPS system, it is believed that the NPSR antagonist will also be promising as a useful therapeutic target in these clinical areas as well.

Applications: Development of a NPSR antagonist for the therapies of alcohol and drug addiction.

Development Status: Early-stage.

Market: More than 700,000 Americans receive alcoholism treatment on any