[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.

FOR FURTHER INFORMATION: 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.

Glial Cell Line-Derived Neurotrophic Factor Opposite Strand (GDNFOS) for Treatment of Neurodegenerative Diseases

Description of Technology: Glial cell line-derived neurotrophic factor (GDNF) is a small human protein encoded by the GDNF gene. GDNF has been effective therapy in laboratory animal models of Parkinson's disease and protects several types of neurons in the brain and peripheral nervous system. The NIDA inventors have discovered primate-specific GDNFOS, encoded by the opposite strand of glial cell derived neurotrophic factor (GDNF) gene. The GDNFOS gene encodes for novel peptides that was found to be reduced in human middle temporal gyrus of Alzheimer's disease brains. These secreted growth proteins have potential neurotrophic activity and they might play a synergistic role in neuroprotective effects of GDNF in human brain. The NIDA inventors have also developed antibody against GDNFOS3 and generated compounds that have potential pharmaceutical use. The compounds consist of GDNFOS nucleic acid transcripts, GDNFOS protein or a functional fragment for treatment of human neurodegenerative diseases.

Potential Commercial Applications:

• Synergistic role in neuroprotective effects of GDNF

• Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, multiple sclerosis and diseases of peripheral organs such as diabetes mellitus type 1

Competitive Advantages:

• Secreted novel growth peptides

• An antibody against GDNFOS3 was developed

Development Stage:

• Early-stage

• Pre-clinical

• In vitro data available

Inventors: Qing-Rong Liu , Mikko Airavaara, Barry Hoffer, Brandon K Harvey (all of NIDA)

Publication: Airavaara M, et al. Identification of novel GDNF isoforms and cis-antisense GDNFOS gene and their regulation in human middle temporal gyrus of Alzheimer disease. J Biol Chem. 2011 Dec 30;286(52):45093-102. [PMID 22081608]

Intellectual Property: HHS Reference No. E-044-2012/0 — US Provisional Application No. 61/619, 296 filed 02 Apr 2012

Licensing Contact: Betty B. Tong, PhD; 301-594-6565; tongb@mail.nih.gov

Collaborative Research Opportunity: The National Institute on Drug Abuse is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize GDNFOS peptide and non-coding RNAs as therapeutic agents for neurodegenerative diseases. For collaboration opportunities, please contact Vio Conley at conleyv@mail.nih.gov.

Increased Therapeutic Effectiveness of Immunotoxins That Use Toxin Domains Lacking Human B-cell Epitopes

Description of Technology: Immunotoxins kill cancer cells while allowing healthy, essential cells to survive. As a result, patients receiving an immunotoxin are less likely to experience the deleterious side-effects associated with non-discriminate therapies such as chemotherapy or radiation therapy. Unfortunately, the continued

administration of immunotoxins often leads to a reduced patient response due to the formation of neutralizing antibodies against immunogenic epitopes contained within Pseudomonas exotoxin A (PE). To improve the therapeutic effectiveness of PE-based immunotoxins through multiple rounds of drug administration, NIH inventors have sought to identify and remove the human B-cell epitopes within PE. Previous work demonstrated that the removal of the murine B-cell and T-cell epitopes from PE reduced the immunogenicity of PE and resulted in immunotoxins with improved therapeutic activity. This technology involves the identification and removal of major human B-cell epitopes on PE by mutation or deletion. Considering these immunotoxins will be administered to humans, the removal of human immunogenic epitopes is important. The resulting PE-based immunotoxins have increased resistance to the formation of neutralizing antibodies, and are expected to have improved therapeutic efficacy.

Potential Commercial Applications:

• Essential component of immunotoxins

• Treatment of any disease associated with increased or preferential expression a specific cell surface receptor

• Specific diseases include hematological cancers, lung cancer, ovarian cancer, breast cancer, and head and neck cancers

Competitive Advantages:

• PE variants now include the removal of human B-cell epitopes, further reducing the formation of neutralizing antibodies against immunotoxins which contain the PE variants.

• Less immunogenic immunotoxins result in improved therapeutic efficacy by permitting multiple rounds of administration in humans.

• Targeted therapy decreases non-specific killing of healthy, essential cells, resulting in fewer non-specific side-effects and healthier patients.

Development Stage: Pre-clinical

Inventors: Ira H. Pastan et al. (NCI)

Publication: Liu W, et al. Recombinant immunotoxin engineered for low immunogenicity and antigenicity by identifying and silencing human B-cell epitopes. Proc Natl Acad Sci USA. 2012 Jul 17;109(29):11782-7. [PMID 22753489]

Intellectual Property: HHS Reference No. E-263-2011/0 — U.S. Provisional Application No. 61/535,668 filed 16 Sep 2011

Related Technologies:

• PCT Patent Publication WO 2011/032022 (HHS Reference No. E-269-2009/0-PCT-02)

• US Patent Publication US 20100215656 A1 (HHS Reference No. E-292-2007/0-US-06)

• US Patent Publication US 20090142341 A1 (HHS Reference No. E-262-2005/0-US-06)

• Multiple additional patent families

Licensing Contact: David A. Lambertson, Ph.D.; 301-435-4632; lambertsond@mail.nih.gov

Collaborative Research Opportunity: The National Cancer institute is seeking statements of capability or interest from parties interested in collaborative research to

further develop, evaluate or commercialize this technology. For collaboration opportunities, please contact John Hewes, Ph.D. at hewesj@mail.nih.gov.

Novel Nitroxyl (HNO) Releasing Compounds and Their Use in Treating Diseases

Description of Technology: Nitroxyl (HNO) is a chemical species that exhibits distinct biological properties in comparison to its oxidized product, nitric oxide (NO). Previous investigations have revealed that the distinct properties of HNO make it a tempting species for wide therapeutic application as it has shown potential in the treatment of heart failure, cancer, and other diseases in various animal and *in vitro* models. Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, are compounds that inhibit cycloxygenase (COX)-mediated conversion of arachidonic acids to prostagladins. NSAIDs are known for their analgesic properties and are therapeutically involved in many physiological functions, including the inhibition of chronic pain and inflammation inhibition, prevention of heart disease, renal function, and cancer. Prolonged use of NSAIDs can lead to serious gastrointestinal and renal side effects, including ulcer perforation, upper gastrointestinal bleeding, and death, which has limited NSAID therapies.

The instant invention described HNO-releasing NSAIDs, which combine the potential therapeutic benefits of HNO and NSAIDs without the toxicities associated with chronic NSAID use. These HNO-releasing NSAIDs provide a reliable controlled release of HNO making them desirable HNO prodrugs. The instant invention disclosed various HNO-releasing NSAIDs and methods of treating or preventing various disorders with

these compositions, such as cardiovascular disorders, cancers, pain, inflammation, and alcoholism.

Potential Commercial Applications:

• Treatment of cancer

• Treatment of cardiovascular disease

• Aversion therapy for alcoholism

Competitive Advantages:

• Combination of therapeutic benefits of HNO and NSAIDs

• Alleviated toxicity associated with chronic NSAID use

• Controlled release of HNO

Development Stage:

• Early-stage

• Pre-clinical

Inventors: David A. Wink and Larry K. Keefer (NCI)

Publication: Miranda KM, et al. Comparison of the NO and HNO donating properties of diazeniumdiolates: primary amine adducts release HNO in vivo. J Med Chem. 2005 Dec 29;48(26):8220-8. [PMID 16366603]

Intellectual Property: HHS Reference No. E-019-2010/2 — International Patent Application PCT/US2011/029072 filed 18 Mar 2011

Licensing Contact: Betty B. Tong, Ph.D.; 301-594-6565; tongb@mail.nih.gov

Polyclonal Antibodies for the Specialized Signaling G protein, Gbeta5

Description of Technology: Researchers at NIDDK have developed polyclonal antibodies against the G protein, Gbeta5. Gbeta5 is a unique and highly specialized G protein that exhibits much less homology than other Gbeta isoforms (~50%) and is preferentially expressed in brain and neuroendocrine tissue. It is expressed prominently in the neuronal cell membrane, as well as in the cytosol and nucleus. Although this distribution pattern suggests that Gbeta5 may shuttle information between classical G protein-signaling elements at the plasma membrane and the cell interior, its function in the brain is largely unknown.

The antibodies were separately generated in rabbits to KLH-conjugates of peptides from the N-terminus of Gbeta5 (antibody ATDG) and the C-terminus of Gbeta5 (antibody SGS). The antibodies can be used for immunoblotting (ATDG, SGS), and immunoprecipitation (ATDG). They can be used to facilitate our understanding of the unique biology and function of Gbeta5 in brain and neurons.

Potential Commercial Applications: These antibodies can be used for research purposes (immunoblotting, immunoprecipitation) by those studying the biology and function of Gbeta5.

Competitive Advantages: Very specific antibodies to study Gbeta5 and G protein signaling.

Development Stage: In vitro data available

Inventors: William Simonds and Jianhua Zhang (NIDDK)

Publications:

1. Zhang JH and Simonds WF. Copurification of brain G-protein beta5 with RGS6 and RGS7. J Neurosci. 2000 Feb 1;20(3):RC59. [PMID 10648734]

2. Zhang JH, et al. Nuclear localization of G protein beta 5 and regulator of G protein signaling 7 in neurons and brain. J Biol Chem. 2001 Mar 30;276(13):10284-9. [PMID 11152459]

3. Zhang S, et al. Selective activation of effector pathways by brain-specific G protein beta5. J Biol Chem. 1996 Dec 27;271(52):33575-9. [PMID 8969224]

4. Zachariou V, et al. An essential role for DeltaFosB in the nucleus accumbens in morphine action. Nat Neurosci. 2006 Feb;9(2):205-11. [PMID 16415864]

Intellectual Property: HHS Reference No. E-192-2006/0 — Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Jaime Greene, M.S.; 301-435-5559; greenejaime@mail.nih.gov

Polyclonal Antibodies for the Gbeta5-associated Regulator of G Protein Signaling Protein, RGS7

Description of Technology: Researchers at NIDDK have developed polyclonal antibodies against the Regulator of G Protein Signalling (RGS) protein, RGS7. RGS7 binds tightly to Gbeta5, a unique and highly specialized G protein that exhibits much less homology than other Gbeta isoforms (~50%). RGS7 is preferentially expressed in brain and neuroendocrine tissue. Like Gbeta5, RGS7 is expressed prominently in the cell membrane, as well as in the cytosol. Although this distribution pattern suggests that complexes containing Gbeta5 and RGS7 may shuttle information between classical G protein-signaling elements at the plasma membrane and the cell interior, the function of the complex in the brain is largely unknown.

The antibodies were generated in rabbits to a glutathione S-transferase (GST) fusion protein with residues 312-469 of bovine RGS7 (antibody 7RC-1) and react with human and rodent RGS7. The antibodies (7RC-1) can be used for immunoblotting and immunoprecipitation. They can be used to facilitate our understanding of the function of Gbeta5/ RGS7 complexes in brain and neurons.

Potential Commercial Applications: These antibodies can be used for research purposes (immunoblotting, immunoprecipitation) by those studying the biology and function of RGS7.

Competitive Advantages: High-titer, multi-epitope antibodies to study RGS7 and RGS7/Gbeta5 complexes and G protein signaling.

Development Stage: In vitro data available

Inventors: William Simonds and Jianhua Zhang (NIDDK)

Publications:

1. Rojkova AM, et al. Ggamma subunit selective G protein beta 5 mutant defines regulators of G protein signaling binding requirement for nuclear localization. J Biol Chem. 2003 Apr 4;278(14):12507-12. [PMID 12551930]

2. Cao Y, et al. Retina Specific GTPase Accelerator RGS11/Gbeta5S/R9AP is a Constitutive Heterotrimer Selectively Targeted to mGluR6 in ON-Bipolar Neurons. J Neurosci 2009 July 22; 29 (29): 9301-13. [PMID 19625520]

3. Anderson GR, et al. Changes in striatal signaling induce remodeling of RGS complexes containing Gbeta5 and R7BP subunits. Mol Cell Biol. 2009 Jun;29(11): 3033-44. [PMID 19332565]

4. Panicker LM, et al. Nuclear localization of the G protein beta5/R7-regulator of G protein signaling protein complex is dependent on R7 binding protein. J Neurochem. 2010 Jun;113(5):1101-12. [PMID 20100282]

Intellectual Property: HHS Reference No. E-077-2011/0 — Research Tool. Patent protection is not being pursued for this technology.

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