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.

Differential Expression of Molecules Associated With Intra-Cerebral Hemorrhage

Description of Technology: Stroke affects 15 million people worldwide each year, and is the number three leading cause of morbidity in the United States. Although most forms of stroke are ischemic in nature, approximately 10–15% of strokes are hemorrhagic. At present, clinical applications for distinguishing between these two forms of stroke do not exist.

The present invention describes a highly predictive, cost-effective diagnostic assay capable of detecting whether an individual has suffered from an intracerebral hemorrhagic stroke and the likelihood of neurological recovery. It comprises a rapid screening device for measuring differential expression patterns of nucleic acid molecules or proteins of at least four hemorrhagic stroke-related genes. Accurate prediction of hemorrhagic stroke will improve rapid diagnosis and aid in determining early treatment regimens.

Applications:

1. Gene expression profile assay for determining hemorrhagic stroke victims.

2. Means of differentiating between hemorrhagic stroke and ischemic stroke thereby optimizing patient response to stroke therapies.

Market:

1. Annually, fifteen billion people suffer from strokes worldwide, and an estimated 700,000 individuals have first-time or recurrent strokes each year in the United States alone.

2. Almost three-fourth of all strokes occur in individuals over 65 years of age.

3. In 2006, the projected indirect and direct costs of stroke are $57.9 billion.

Development Status: This technology requires clinical validation studies.

Inventors: Alison Baird (NINDS) *et al.*

Patent Status: U.S. Provisional Application No. 60/807,027 filed 11 Jul 2006 (HHS Reference No. E–197–2006/0–US–01).

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

Licensing Contact: Fatima Sayyid, M.H.P.M.; 301/435–4521; *sayyidf@mail.nih.gov.*

Collaborative Research Opportunity: NINDS is also seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize this assay for determining hemorrhagic stroke victims. For additional information, please contact: Heather Gunas, J.D., M.P.H; NINDS c/o NCI TTB; 6120 Executive Blvd., Suite 450, Rockville, MD 20852; Phone: 301–451–3944; Fax: 301–402–2117; E-mail: *gunash@mail.nih.gov.*

Diagnosis and Prognosis of Fabry Disease by Detecting Neuronal Apoptosis Inhibitor Protein (NAIP) Expression

Description of Technology: Fabry disease is a severe metabolic disorder that affects the vascular system of multiple tissues and organs. An estimated 1 in 40,000 individuals inherit this rare disease, and suffer from various complications including stroke, renal failure, and cardiac arrest. At present, molecular markers that directly measure cellular dysfunction to not exist, thus, prognosis for Fabry disease therapy can not be assessed.

Available for licensing and commercial development is a rapid diagnostic assay to identify individuals with Fabry disease and an effective mechanism of evaluating enzyme replacement therapy. It provides a quick, inexpensive device for determining expression patterns of the neuronal apoptosis inhibitor protein (NAIP). Peripheral blood white cells of Fabry disease patients are analyzed for elevated levels of the marker NAIP, which is over-expressed in patients suffering from acute strokes. These elevated levels have been found in children with Fabry disease and point to the need for preventive therapies. Additionally, this test can be routinely utilized for evaluation of specific and non-specific therapies that aid in minimizing the complications associated with Fabry disease.

Applications:

1. Rapid diagnostic test to identify person at risk for Fabry disease.

2. Reliable diagnostic test to identify subject response to Fabry disease therapy.

Market: Individuals genetically susceptible to Fabry disease.

Development Status: This technology requires analytic validation.

Inventors: Raphael Schiffmann (NINDS) et al.

Related Publications:

1. DF Moore, H Li, N Jeffries, V Wright, RA Cooper Jr, A Elkahloun, MP Gelderman, E Zudaire, G Blevins, H Yu, E Goldin, AE Baird. Using peripheral blood mononuclear cells to determine a gene expression profile of acute ischemic stroke: a pilot investigation. Circulation. 2005 Jan 18; 111(2):212–221.

2. Y Okada, H Sakai, E Kohiki, E Suga, Y Yanagisawa, K Tanaka, S Hadano, H Osuga, JE Ikeda. A dopamine D4 receptor antagonist attenuates ischemia-induced neuronal cell damage via upregulation of neuronal apoptosis inhibitory protein. J Cereb Blood Flow Metab. 2005 Jul; 25(7):794–806.

3. N Inohara, M Chamaillard, C McDonald, G Nuñez. NOD–LRR proteins: role in host-microbial interactions and inflammatory disease. Annu Rev Biochem. 2005 Jul; 74:355–383.

Patent Status: U.S. Provisional Application No. 60/806,295 filed 30 Jun 2006 (HHS Reference No. E–196–2006/0–US–01).

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

Licensing Contact: Fatima Sayyid, M.H.P.M.; 301/435–4521; *sayyidf@mail.nih.gov.*

Novel Treatment of Vascular Cognitive Impairment

Description of Technology: Available for licensing are methods and formulations for treating or preventing Vascular Cognitive Impairment (VCI) through mucosal administration of E-selectin, an inducible adhesion molecule on endothelial cells. Vascular dementia is defined as the loss of cognitive function resulting from ischemic, ischemic-hypoxic, or hemorrhagic brain lesions as a result of cerebrovascular diseases and pathologic

changes. Presently no adequate medical treatment exists for VCI.

Cerebrovascular disease causes proinflammatory cytokines such as IL–1 and TNF to induce the expression of E-selectin on human endothelium. E-selectin mediates the adhesion of various leukocytes, including neutrophils, monocytes, eosinophils, natural killer cells, and a subset of T cells to the activated endothelium. Activation of vascular endothelial cells by proinflammatory cytokines is believed to be involved in conversion of the luminal surface of endothelium from anticoagulant and anti-inflammatory to procoagulant and pro-inflammatory. These vascular changes are thought to underlie the development of VCI.

Mucosally administered antigens can inhibit immune responses in an antigen specific fashion by inducing a subset of lymphocytes to produce anti-inflammatory cytokines in the presence of the antigen. This type of tolerance has been termed ''bystander suppression''. In an animal model of VCI, intranasal administered E-selectin suppressed activation of vessel segments beginning to express E-selectin and thus prevented the development of VCI. Immunosuppression via antigen-specific modulation of the immune response (mucosal tolerance) should have no systemic immunosuppressive effects.

Inventors: John M. Hallenbeck *et al.* (NINDS).

Patent Status: U.S. Provisional Application No. 60/712,359 filed 30 Aug 2005 (HHS Reference No. E–271–2005/0–US–01).

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

Licensing Contact: Norbert Pontzer, Ph.D., J.D.; 301/435–5502; *pontzern@mail.nih.gov.*

Collaborative Research Opportunity: The NINDS Stroke Branch is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize the use of E-selectin for treatment of VCI. For more information, please contact: Laurie Arrants, NINDS Technology Transfer Office, 301–435–3112; *arrantsl@ninds.nih.gov.*

Use of LCAT To Reduce Cholesterol and Prevent Atherosclerosis

Description of Technology: Available for licensing and commercial development is a method of decreasing accumulation of cholesterol in arteries of humans by administering lecithin-cholesterol acyltransferase (LCAT). This method is useful for the therapeutic treatment of subjects at risk for developing atherosclerosis.

High plasma concentration of HDL cholesterol is associated with reduced risk of cardiovascular diseases (such as ischemic stroke and myocardial infarction). In contrast, low levels of HDL are associated with increased risk of atherosclerotic diseases. The plasma protein enzyme LCAT plays a critical role in the metabolism of HDL and it facilitates the removal of cholesterol from the body. Individuals with a mutation in the LCAT gene have low HDL plasma levels and exhibit an increased risk for atherosclerosis.

Therefore, upregulation of LCAT function has been proposed as an HDL–C increasing therapy, and may have atheroprotective effects. This invention provides for several methods of administering LCAT polypeptide to decrease cholesterol accumulation in arteries.

Development Status: Animal data available.

Inventors: Silvia Santamarina-Fojo, Jeffrey M. Hoeg, H. Bryan Brewer (NHLBI).

Relevant Publication: JM Hoeg *et al.* Overexpression of lecithin:cholesterol acyltransferase in transgenic rabbits prevents diet-induced atherosclerosis. Proc Natl Acad Sci USA. 1996 Oct 15;93(21):11448–11453.

Patent Status: U.S. Patent No. 6,635,641 issued on 21 Oct 2003 (HHS Reference No. E–007–1996/0–US–03); PCT Application No. PCT/US96/18159 filed 09 Sep 1996, which was published as WO 1997/17434 on 15 May 1997 (HHS Reference No. E–007–1996/0–PCT–02); Australian Patent No. 728257 issued on 19 Apr 2001; and National Stage filings in Canada and Europe.

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

Licensing Contact: *NIHOTT@mail.nih.gov*; 301/496–7057.

Devices for Aseptic Lyophilization of Biological Samples

Description of Technology: Biological materials are often lyophilized and stored in small aliquots for long-term preservation as a means of improving stability and expanding shelf life. At present, sterility of solutions cannot be preserved throughout the lyophilization process, and reconstituted samples must be filtered to remove contaminants such as fungi or bacteria, resulting in considerable loss of expensive sample via absorption by the filter. Thus, there exists a need for a device that eliminates microbial contamination throughout the lyophilization process and provides materials that are ready to use following lyophilization.

This technology offers a functional method to prevent microbial contamination during lyophilization and a simple means to prevent contamination. It affords a convenient system for gas venting and exchange utilizing a microcentrifuge tube fitted with a cap incorporating a filter membrane. In a related technology, a unique, cost-effective multi-well plate assembly provides for simultaneous lyophilization of small sample volumes for high-throughput operations. Thus, these technologies are well-suited for researchers concerned about contamination during the lyophilization process. Given the spillage often occurring within centrifugal freeze-dryers, these technologies are also useful even when sterility is not needed, as they prevent contamination from the often-dirty interiors of laboratory centrifugal freeze-dryers, as well as cross-contamination between samples undergoing lyophilization. In addition, by extending shelf-lives, these technologies enable researchers to purchase expensive biomolecules and pharmaceuticals in money-saving bulk quantities. Furthermore, these technologies permit cells to be grown and stored axenically, in small quantities, with or without lyophilization.

Applications:

1. Maximizes the shelf-lives of expensive biomolecules and pharmaceuticals.

2. Makes practical the bulk purchase of expensive biomolecules and pharmaceuticals by extending shelf-lives.

3. Makes possible the axenic storage of cells via aseptic freeze-drying.

4. Makes possible the production and use of small, sterile aliquots of precious materials by eliminating unnecessary filtration steps.

5. Makes possible the sterile growth of cells in small volumes.

Market:

1. Researchers worldwide who utilize sterile, labile compounds.

2. Researchers who utilize microbial, plant, or animal cell cultures.

Development Status: Development is complete and invention has been successfully tested.

Inventors: Geoffrey Kidd (NCI).

Patent Status: U.S. Patent 5,958,778 issued 28 Sep 1999 (HHS Reference No. E–015–1995/2–US–01); U.S. Patent 6,503,455 issued 07 Jan 2003 (HHS Reference No. E–015–1995/2–US–02); U.S. Patent Application 10/238,147 filed 09 Sep 2002 (HHS Reference No. E–304–2003/0–US–01).

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

Licensing Contact: *NIHOTT@mail.nih.gov*; 301/496–7057.

Dated: August 29, 2006.

Steven M. Ferguson,

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

[FR Doc. E6–14753 Filed 9–6–06; 8:45 am]

BILLING CODE 4140–01–P

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Oligo Microarray for Detection of All Known Mammalian and Avian Pathogenic Viruses

Description of Technology: The spectrum of pathogenic viruses of importance in human disease, agriculture and biology is not only large and diverse, but continually evolving. The identification or isolation of viral pathogens, in correlation with the presence of specific disease phenotypes, is of paramount importance both to diagnosis of disease and the subsequent management or treatment of viral infection. The limitations of current viral detection methods, such as PCR and immunoassays, led to the development of a novel microarray system for specific detection of viruses. The technology offered here for licensing provides a method for high-throughput screening of known pathogenic viruses along with identification of ''new'' disease-associated viruses.

The novel method is based on a viral microarray containing 10,000 immobilized DNA oligonucleotide features, representing all known mammalian and avian pathogenic viruses (approximately 600). Software was also developed to analyze the viral microarray results. The oligonucleotide features in this system are 60-mer long and distributed across both conserved and non-conserved regions of known viral sequences. This design serves the dual purpose of: (1) Facilitating validation via redundant signals associated with each represented virus and (2) allowing for the discovery of new viruses, which arise due to recombination. In addition, positive and negative controls against human and mouse housekeeping genes are included along with software for analysis of virus microarray results.

Further advantages of the viral microarray include: (a) The use of sample inputs as little as 10ng of either total DNA or RNA extracted from virus infected cells, representing as few as 20 viral particles; (b) detection of viruses of both DNA and RNA classes; (c) a capacity for high-throughput screening of various sample types including serum, saliva and biopsy tissues; and (d) analysis of a large number of samples in parallel on identical arrays.

The detection of viral DNA is unique to this technology, as other available technologies only detect viral genomic RNA or viral mRNA transcripts. Additionally, the viral chip was found to be highly specific and sensitive for detecting different viral genomic sequences in cell lines and multiple viral constructs co-infection in cultured cells.

Applications: (1) Detection and identification of viruses that cause disease; (2) Efficient discovery of new pathogenic viruses; (3) Diagnosis of human and animal disease outbreaks; (4) Identification of viral agents used in bioterrorism.

Development Status: (1) The pre-clinical performance of the viral microarray was evaluated by application of four virally positive infected cell lines (JSC–1-harboring EBV and KSHV, BCBL–1 harboring KSHV, HeLa-harboring HPV18, Cem X 174 harboring SIV). (2) Clinical performance was tested and validated through analysis of total RNA from cold (swab), Japanese Encephalitis, Dengue, Ebola and West Nile virus samples.

Inventors: Cassio S. Baptista (NCI), Xiaolin Wu (NCI), David J. Munroe (NCI).

Patent Status: U.S. Provisional Application No 60/797,334 filed 02 May 2006 (HHS Reference No. E–206–2006/0–US–01).

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

Licensing Contact: Cristina Thalhammer-Reyero, PhD, MBA; 301/435–4507; *thalhamc@mail.nih.gov*

Collaborative Research Opportunity: The NCI-Laboratory of Molecular Technology is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize this oligo microarray for identification and detection of all known mammalian and avian pathogenic viruses. Please contact Betty Tong, PhD at 301–594–4263 or *tongb@mail.nih.gov* for more information.

Novel Monoclonal Antibody Microarray

Description of Technology: Gene expression profiling at the mRNA level has proven to be a powerful and useful tool, however this approach suffers from inherent limitations: (1) The mRNA abundance does not typically correlate well with protein abundance and (2) protein structure, activity, and function can be altered and regulated by post-translational modifications. Thus, there is growing recognition that these approaches should be complemented by profiles of the gene products or proteins themselves. The present invention provides methods for constructing and using a novel Monoclonal Antibody Microarray which allows high-throughput determination of protein expression profiles from serum, tissue, and cultured cells.

The Monoclonal Antibody Microarray consists of more than 1000 different antibodies immobilized on a glass slide, which recognize antigens from several groups of proteins, including cytokines, kinases, apoptotic proteins, growth factor receptors, tumor suppressors, and oncoproteins. Protein samples to be identified and quantified are labeled with fluorescence and hybridized to the antibodies immobilized on the arrays. By differentially labeling two protein samples (dual-color labeling) and co-hybridizing to the same microarray, a direct comparative analysis of protein expression can be performed using as little as 100 μg of total protein. This method allows a large number of samples to be screened in parallel on identical arrays.

Applications: (1) High-throughput analysis of protein expression; (2) Direct measurement of protein expression at