[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.

Optical Microscope Software for Breast Cancer Diagnosis

Description of Technology: The instant invention discloses a software to analyze optical microscopic images of human breast tissue sections for diagnosing cancer by using the differences in spatial positioning of certain genes. The software uses the inherent hierarchy in the data and stores all the analysis and manual interaction information in a highly structured XML file. It is a user-friendly software to discriminate normal and cancerous human breast tissue section images that can be used for large experiments. Additionally the software uses a cluster of computers in the background to reduce the analysis time for large image datasets. Furthermore, the software of instant invention provides a set of tools for performing diagnostic or prognostic assays on new unseen datasets.

Potential Commercial Applications:

• The software could be an essential part of an integrated diagnostic or prognostic assay for breast cancer detection.

• The software could be a key tool for biomedical research to test new markers and their applicability for diagnostic purposes.

• The use of the software could provide important information for understanding the underlying causes of gene repositioning.

Competitive Advantages:

• The software of instant invention can be used to analyze relatively large datasets.

• To reduce the processing time by at least10 fold.

• The software can be used in a broad range of quantitative image analysis applications.

Development Stage:

• Prototype

• Clinical

• In vitro data available (human)

Inventors: Kaustav Nandy (SAIC-Frederick, Inc), Stephen J. Lockett (SAIC-Frederick, Inc), Prabhakar R. Gudla (SAIC-Frederick, Inc), William Cukierski (NCI), Renee Qian (NCI), Karen J. Meaburn (NCI), Tom Misteli (NCI)

Publications:

1. Gudla PR, et al. A high-throughput system for segmenting nuclei using multiscale techniques. Cytometry A. 2008 May;73(5):451-66. [PMID 18338778]

2. Nandy K, et al. Automatic nuclei segmentation and spatial FISH analysis for cancer detection. Conf Proc IEEE Eng Med Biol Soc. 2009;2009:6718-21. [PMID 19963931]

3. Meaburn KJ, et al. Disease-specific gene repositioning in breast cancer. J Cell Biol. 2009 Dec 14;187(6):801-12. [PMID 19995938]

4. Cukierski WJ, et al. Ranked retrieval of segmented nuclei for objective assessment of cancer gene repositioning. BMC Bioinformatics. 2012 Sep 12;13:232. [PMID: 22971117]

5. Nandy K, et al. Supervised learning framework for screening nuclei in tissue sections. Conf Proc IEEE Eng Med Biol Soc. 2011;2011:5989-92. [PMID 22255704]

Intellectual Property: HHS Reference No. E-286-2012/0 — Software. Patent protection is not being pursued for this technology.

Licensing Contact: Susan Ano, Ph.D.; 301-435-5515; anos@mail.nih.gov

Collaborative Research Opportunity: The SAIC-Frederick Optical Microscopy and Analysis Laboratory 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.

Simple Direct Zirconium-89 Cell PET Label, ^{89}Zr-Labeled Cells, and Methods for Real-time In Vivo Pet Imaging

Description of Technology: The capability to image cells and cellular processes in real time over a scale of days could dramatically improve research insights and the effectiveness of cell-based therapies. Zirconium-89 (^{89}Zr) has a half-life of over three days (78.4 hours) over 44 times longer compared to Fluorine (^{18}F) the most commonly used PET isotope (half-life of 1 hour and 50 minutes). ^{89}Zr is also advantageous compared to other long half-life isotopes because it is not limited by high background activity and cell toxicity. Labeling cells with ^{89}Zr, is currently accomplished by indirect methods using secondary cell-type specific reagents such as antibodies. This technology is a PET imaging complex of ^{89}Zr and polycation that is internalized by the cells. This complex has been able to directly label a wide range of cells, without the use of secondary reagents. ^{89}Zr-labeled cells of lymphocytic lineage, including T cells, natural killer T-cells, macrophages, dendritic cells, and stem cells, have been produced and

imaged in vivo with minimal damage to the cells. This PET imaging agent can be readily combined with an MR imaging agent for combined PET/MR imaging of cells. The imaging capabilities enabled by this technology may significantly improve cell therapies, cell level diagnostics and aid research for non-cell based therapies.

Potential Commercial Applications:

• Imaging

• Diagnostic

• Cell therapies

• Transplantation and transfusion

Competitive Advantages:

• Direct labeled cells (versus indirect techniques)

• Longer half-life

• Not limited by high background activity and cell toxicity

Development Stage:

• Early-stage

• Pre-clinical

• In vivo data available (animal)

Inventors: Omer Aras (CC), Peter Choyke (NCI), Joseph Frank (CC), Noriko Sato (CC), Jeremy Pantin (NHLBI)

Intellectual Property: HHS Reference No. E-056-2012/0 — US Provisional Application No. 61/611964 filed 16 Mar 2012

Licensing Contact: Tedd Fenn; 301-435-5031; Tedd.Fenn@nih.gov

Collaborative Research Opportunity: The NCI 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.

Small, Stable, Functional, Soluble, Monomeric IgG1 Fc Molecules Engineered Therapies

Description of Technology: This technology relates to small (~27 kDa) antibody fragments that are potentially useful for therapeutic development. These are monomeric IgG fragment crystalizable (mFc) compositions; they are long half-lived, functional (pH dependent binders of neonatal Fc receptor - FcRn); and they are soluble and express efficiently in E. coli. These molecules may serve as a platform for development of engineered mFc-based antibodies and fusion proteins with therapeutic applications. Efforts to engineer antibody-based therapeutics, to date, have encountered technical limitations due to the relatively large fragment size and short fragment half-life. The IgG fragment crystalizable (Fc) is a dimer of two constant domains (CH2-CH3 chains). Fc has a long half-life, which makes it promising as a candidate for engineering antibody therapeutics. Fusion proteins based on Fc dimer molecules demonstrate extended half-life, due to the ability to bind FcRn at acidic pH. However, the relatively large size of the Fc domains (~50 kD) is not optimal. This technology uses smaller (~27 kDa) mFc compositions that retain efficient binding to human FcRn and demonstrate long half-life. These mFc compositions are promising for the development of novel therapeutics because the smaller size may allow for superior access to targets and tissues compared to

full sized mAbs and larger fragment-based therapeutics, while also retaining important function characteristics.

Potential Commercial Applications: Therapeutics - human and veterinary, engineered antibody and fusion proteins.

Competitive Advantages: Smaller size results better tissue penetration, reduced steric hindrance, increased therapeutic efficiency and lower cost.

Development Stage:

• Early-stage

• Pre-clinical

Inventors: Dimiter S. Dimitrov and Tianlei Ying (NCI)

Publication: Ying T, et al. Soluble monomeric IgG1 Fc. J Biol Chem. 2012 Jun 1; 287(23):19399-408. [PMID 22518843]

Intellectual Property: HHS Reference No. E-019-2012/0 — U.S. Patent Application No. 61/612,138 filed 16 Mar 2012

Related Technologies: HHS Reference No. E-003-2007/0 —

• U.S. Patent Application No. 61/063,245 filed 31 Jan 2008

• PCT Application No. PCT/US2009/0326 and related international applications filed on 30 Jan 2009 in Australia, Canada, China, Europe, Japan, and India

• U.S. Patent Application No. 12/864,758 filed 27 Jul 2010

Licensing Contact: Tedd Fenn; 301-435-5031; Tedd.Fenn@nih.gov

Collaborative Research Opportunity: The NCI/CCR/NP is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize Small, Stable, Functional, Soluble, Monomeric IgG1

Fc Molecules Engineered Therapies. For collaboration opportunities, please contact John Hewes, Ph.D. at hewesj@mail.nih.gov.

Virus-Like Particles Mediated Protein and RNA Delivery

Description of Technology: The invention is directed to novel virus-like particles (VLPs) that are capable of binding to and replicating within a target mammalian cell, including human cells. The claimed VLPs are safer than viral delivery because they are incapable of re-infecting target cells. The present VLPs can optionally comprise inhibitory recombinant polynucleotides, such as microRNA, antisense RNA or small hairpin RNA, to down regulate or turn off expression of a particular gene within the target cell. Alternatively, recombinant polynucleotides packaged within VLPs can comprise a gene encoding a therapeutic protein so as to enable expression of that protein within the target cell. Specifically, VLPs of the invention are composed of an alphavirus replicon that contains a recombinant polynucleotide, a retroviral gag protein, and a fusogenic envelope glycoprotein.

While the claimed VLPs have a variety of applications, therapeutic uses of the VLPs include directing antibody synthesis and converting cancer cells into antigen presenting cells. Additional applications include using VLPs to induce fast (approx. 3-4 hrs) and high levels of protein production in mammalian cells.

Potential Commercial Applications:

• Delivery of microRNA and small hairpin RNA to reduce express of targeted genes in a human cell

• Delivery of coding RNA for robust expression in mammalian systems

• Direct antibody production by in vivo injection of replicons (no antigen purification)

• Therapeutic applications

Competitive Advantages:

• High level (~million copies per cell) of RNA production/synthesis within target cell

• Fast expression (approx. 3-4 hrs compared to 1-2 days) following VLP introduction into target cells

• Obviates need to use expensive antigen purification for proteins or antigens produced inside target cells

Development Stage:

• Pilot

• Pre-clinical

• In vitro data available

• In vivo data available (animal)

Inventors: Stanislaw J. Kaczmarczyk and Deb K. Chatterjee (NCI)

Intellectual Property: HHS Reference No. E-264-2011/0 — US Application No. 61/615,687 filed 26 Mar 2012

Licensing Contact: Lauren Nguyen-Antczak, Ph.D., J.D.; 301-435-4074; lauren.nguyen-antczak@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 Novel Delivery of Packaged RNA to

Mammalian Cells. For collaboration opportunities, please contact Kevin Brand at brandk@mail.nih.gov.

A Combinatorial Cloning Platform for Construction of Expression Vectors for Protein Production

Description of Technology: The Combinatorial Cloning Platform (CCP) of this invention is a collection of vectors for use with the Gateway Multisite Recombination System (Life Technologies). The CCP that is currently available includes plates of 192 glycerol stocks of *E. coli* each containing one of the library plasmids, and a collection of 24 DNAs that are the downstream vectors for expression in different hosts. Uses of this CCP include construction of protein expression constructs with various fusion tags, generation of expression constructs with different promoters for *in vivo* expression, and production of clones with fluorescent tags for localization experiments. The advantage of the CCP is based on the exquisite specificity of the Multisite Gateway reactions, which permit linkage of multiple elements in a directional fashion and involve no additional DNA amplification. There is also no need for restriction-based cloning processes, which have a high rate of failure and may require optimization depending on the sites available in a given clone. The CCP library includes clones for fluorescent and luminescent reporters, epitope and solubility fusion tags, bimolecular fluorescence complementation (BiFC) fusions, 18 different eukaryotic promoters, and many other useful clones. In addition, the destination vector collection contains two flavors of Gateway destination vectors for *E. coli*, baculovirus, mammalian, and lentiviral expression.

Potential Commercial Applications:

• Construction of protein expression constructs with various fusion tags

• Generation of expression constructs with different promoters for in vivo expression

• Production of clones with fluorescent tags for localization experiments

• Generation of constructs for making mutant cell lines or transgenic animals

• Production of vectors for shRNA or miRNA delivery

Competitive Advantages: The CCP is considerably more flexible than currently available commercial systems for construction of protein expression constructs.

Development Stage:

• Prototype

• Pre-clinical

• In vitro data available

Inventor: Dominic Esposito (NCI)

Publication: Hopkins RF, et al. Optimizing transient recombinant protein expression in mammalian cells. Methods Mol Biol. 2012;801:251-68. [PMID 21987258]

Intellectual Property: HHS Reference No. E-164-2011/0 — Research Tools. Patent protection is not being pursued for these technologies.

Licensing Contact: Suryanarayana Vepa, Ph.D., J.D.; 301-435-5020; vepas@mail.nih.gov

Therapeutic Peptide Treatment for Dyslipidemic and Vascular Disorders

Description of Technology: This invention is directed to use of certain peptide analogs comprising multiple amphipathic helical domains that are able to promote

cellular lipid efflux and stimulate lipoprotein lipase activity. As a result, administration of invention peptides lead to reduced incidences of hypertriglyceridemia without inducing toxicity. Existing peptides that stimulate efflux of lipids from cells exhibit unacceptably high toxicity. Invention peptides are superior to existing peptides and can also be used to treat or prevent a vast range of vascular diseases, and their dyslipidemic precursors. Exemplary vascular diseases and conditions that could benefit from treatment with the invention peptides include: dyslipidemia, hyperlipidemia, hypercholesterolemia, HDL deficiency, coronary heart disease, atherosclerosis, and thrombic stroke.

Potential Commercial Applications:

• Treatment of dyslipidemic and vascular disorders

• Method of identifying therapeutic non-cytotoxic peptides

Competitive Advantages:

• Specific control of lipid efflux and transport

• Transient hypertriglyceridemia with no reported toxicity

Development Stage:

• Early-stage

• Pre-clinical

• In vitro data available

• In vivo data available (animal)

Inventors: Alan T Remaley and Marcelo A Amar (NHLBI)

Publications:

1. Remaley AT, et al. Synthetic amphipathic helical peptides promote lipid efflux from cells by an ABCA1-dependent and an ABCA1-independent pathway. J Lipid Res. 2003 Apr;44(4):828-36. [PMID 12562845]

2. Sviridov DO, et al. Helix stabilization of amphipathic peptides by hydrocarbon stapling increases cholesterol efflux by the ABCA1 transporter. Biochem Biophys Res Commun. 2011 Jul 8;410(3):446-51. [PMID 21672528]

3. Osei-Hwedieh DO, et al. Apolipoprotein mimetic peptides: Mechanisms of action as anti-atherogenic agents. Pharmacol Ther. 2011 Apr;130(1):83-91. [PMID 21172387]

Intellectual Property: HHS Reference No. E-138-2008/0 — US Patent Application No. 12/937,974 filed 14 Oct 2010

Licensing Contact: Lauren Nguyen-Antczak, Ph.D., J.D.; 301-435-4074; lauren.nguyen-antczak@nih.gov

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Date

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