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.

Monoclonal Antibodies Against Bordetella pertussis Filamentous Hemagglutinin (FHA) Protein

Description of Technology: Filamentous hemagglutinin (FHA) is one of the major adhesion molecules of *Bordetella pertussis*, a bacterial infection that causes whopping cough. Once thought to be primarily a childhood disease, *B. pertussis* infection shows an increasing incidence among adults as well as infants. Recent CDC reports show an almost 19-fold increase in the number of cases among 10–19 year olds and an almost 16-fold increase among those 20 and older. These data underscore the need for a new generation of vaccines and detailed studies focused on the pathways of *B. pertussis* infectivity.

Available for licensing are three hybridoma cell lines capable of expressing monoclonal antibodies against FHA. ELISA and Western blot analyses have shown that these antibodies, map to specific epitopes, can successfully bind to FHA as well as prevent binding of the purified FHA to various cells. The additional studies showed that one antibody was able to prevent the adhesion of *B. pertussis* to epithelial cell monolayers. These findings show that monoclonal antibodies expressed in featured hybridoma cell lines can be successfully used for studies of infectivity mechanisms as well as development of new diagnostics and acellular vaccines against *B. pertussis*.

Applications:

- New generation of diagnostics.
- Acellular vaccine development.

Inventor: Michael Brennan (CBER/FDA).

Relevant Publications:

1. Leininger E, Probst PG, Brennan MJ, Kenimer JG. Inhibition of Bordetella pertussis filamentous hemagglutinin-mediated cell adherence with monoclonal antibodies. FEMS Microbiol Lett. 1993 Jan 1;106(1):31–38.

2. Leininger E, Bowen S, Renauld-Mongénie G, Rouse JH, Menozzi FD, Locht C, Heron I, Brennan MJ. Immunodominant domains present on the Bordetella pertussis vaccine component filamentous hemagglutinin. J Infect Dis. 1997 Jun;175(6):1423–1431.

Patent Status: HHS Reference No. E–044–2008/0—Research Tool. Patent protection is not being sought for this technology.

Licensing Status: Available for non-exclusive licensing.

Licensing Contact: Susan Ano, PhD; 301–435–5515; *anos@mail.nih.gov.*

Automated Method for Rapid Detection of Sickle Cell Disease Inhibitors

Description of Technology: Available for licensing is a rapid and automated method for discovering potential drugs for the treatment of sickle cell anemia by determining the sickling times for a large population of red blood cells. The method uses a combination of laser photolysis and statistical processing of digital images. Sickle cell disease is an inherited disorder that affects over 70,000 Americans. The disease is characterized by presence of mutant hemoglobin S in red blood cells, which polymerizes to form fibers when deoxygenated. Such fibers lead to distortion of red blood cells into the shape of a sickle and alter the mechanical properties of these cells. Studies demonstrate that the time to polymerization involves a delay time and rapid growth phase and is particularly sensitive to hemoglobin concentration. As a result, identification of drugs that inhibit sickle cell disease is accomplished using an assay for delay times for populations of red blood cells. The invention creates a uniform time at which polymerization is initiated for all red blood cells in the sample region and accurately determines the time at which cellular distortion begins for each cell. Potential drugs are those compounds that significantly increase the delay time of sickling time, *i.e.* the time at which the cell changes shape due to intracellular polymerization.

Applications:

- Rapid automated detection of compounds that inhibit sickling and are therefore potential drugs for sickle cell disease.
- Objective assay for monitoring disease severity.

Development Status: The technology is capable of determining the distribution of cellular delay times in a large number of samples in series in a 48 well plate format

Inventors: Jeffrey F. Smith, H. James Hofrichter, and William A. Eaton (NIDDK).

Patent Status:

- U.S. Patent Application No. 11/652,843, filed 11 Jan 2007 (HHS Reference No. E–021–2007/0–US–01).
- PCT Application No. PCT/US2008/000427 filed 11 Jan 2008 (HHS Reference No. E–021–2007/0–PCT–02).

Licensing Status: Available for licensing.

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

Collaborative Research Opportunity: The NIDDK Laboratory of Chemical Physics is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize this technology. Please contact Rochelle S. Blaustein, J.D. at 301–451–3636 or *rochelle.blaustein@nih.gov* for more information.

Dated: September 9, 2008.

Richard U. Rodriguez,

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

[FR Doc. E8–21505 Filed 9–15–08; 8:45 am]

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Bifunctional Compounds That Bind to Hormone Receptors

Description of Technology: The development and progression of prostate cancer is dependent on the androgen receptor (AR), a ligand-dependent transcription factor. In the inactive form AR resides in the cytosolic region of the cell and when activated, AR is imported into the nucleus. Initial hormonal therapy for prostate cancer involves lowering serum levels of testosterone to shut down AR activity. Despite initial patient responses to testosterone-depleting therapies, prostate cancer becomes refractory to hormonal therapy. Notably, AR is reactivated in hormone-refractory prostate cancer and reinstates its proliferative and survival activity.

Available for licensing is a novel chemical compound which is bifunctional and binds to AR. This compound is comprised of tubulin-binding and steroid receptor-binding moieties. This compound is designed to antagonize AR function in a nonclassical manner by several mechanisms and kills hormone-refractory prostate cells better than both functional moieties. This compound is a first-in-class of bifunctional steroid receptor binding agents that can antagonize steroid receptors in a variety of hormone-dependent diseases, such as breast and prostate cancer.

Applications:

• Therapeutic compounds that selectively target steroid receptor-expressing cancer cells resulting in minimal patient toxicity.

• Method to treat hormone resistant prostate cancer and potentially other steroid receptor dependent diseases such as breast cancer.

Market:

• Prostate cancer is the second most common type of cancer among men, wherein one in six men will be diagnosed.

• An estimated 186,320 new diagnosed cases and 28,660 deaths due to prostate cancer in the U.S. will occur in 2008.

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

Inventors: Nima Sharifi *et al.* (NCI).

Publication: N Sharifi *et al.* A bifunctional colchicinoid that binds to the androgen receptor. Mol Can Ther. 2007 Aug;6(8):2328–2336.

Patent Status: PCT Application No. PCT/US2008/008299 filed 02 Jul 2008, claiming priority to 03 Jul 2007 (HHS Reference No. E–163–2007/0–PCT–02).

Availability: Available for exclusive or non-exclusive licensing.

Licensing Contact: Jennifer Wong; 301–435–4633; *wongje@mail.nih.gov.*

Vitamin D Receptor Antagonists for Treating Breast Cancer

Description of Technology: Vitamin D receptor (VDR) is a nuclear receptor that is activated by calcitriol, the active form of vitamin D. It is best known for regulating dietary calcium uptake necessary for bone growth, but it also affects cell proliferation and differentiation. Therefore, it was thought that treatment with calcitriol or its derivatives could be useful to treat the uncontrolled proliferation typical of cancer cells. However, this approach has been unsuccessful to date because it leads to toxic levels of calcium in the blood.

This invention relates to derivatives of calcitriol that can block cell growth without harmfully raising calcium levels. Specifically, these compounds act as antagonists of VDR blocking its ability to stimulate cell proliferation. This technology can be useful in treating breast cancer or other malignancies.

Applications:

• Potential drugs for treating breast cancer and possibly also prostate cancer, colorectal cancer, leukemia, melanoma, or glioma.

• Prevention of cancer in high-risk population.

• Research on vitamin D receptor functions and cancer.

Market: About 182,460 American women will be diagnosed with invasive breast cancer in 2008.

Development Status: Pre-clinical data available.

Inventors: Julianna Barsony (NIDDK).

Publication: J Barsony *et al.* Development of a biologically active fluorescent-labeled calcitriol and its use to study hormone binding to the vitamin D receptor. Anal Biochem. 1995 Jul 20;229(1):68–79.

Patent Status: U.S. Patent No. 7,361,664 issued 22 Apr 2008 (HHS Reference No. E–213–2001/2–US–02).

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

Licensing Contact: Whitney Hastings; 301–451–7337; *hastingw@mail.nih.gov*.

A Novel Recombinant Immunotoxin SS1P (anti-mesothelin dsFv-PE38): A Therapeutic Treatment for Lung Cancer and Other Mesothelin Expressing Cancers

Description of Technology: Mesothelin is a cell surface glycoprotein whose expression is largely restricted to mesothelial cells in normal tissues. Significantly, mesothelin is also highly expressed in many cancers (including malignant mesothelioma, ovarian cancer, lung cancer, pancreatic carcinomas, gastric carcinomas, etc.). As a result, mesothelin is an excellent target for immunotherapy.

NIH inventors have generated high affinity antibodies to mesothelin (SS1) and fused them to various functional fragments of *Pseudomonas* Exotoxin A (PE) to produce the immunotoxin SSIP. New SS1P constructs include PE fragments and mutants with reduced immunogenicity, resulting in immunotoxins with greater efficacy. SS1P activity was previously shown in patients suffering from mesothelioma and ovarian cancer; laboratory studies now demonstrate cytotoxicity against lung carcinoma cells. Additionally, SS1P has shown synergy with front line cancer therapeutics in a mouse model, making SS1P an excellent candidate both a stand-alone therapeutic and a combination therapeutic.

Applications:

• SS1P can be used as a therapy for mesothelin expressing cancers, including mesothelioma, ovarian cancer and lung adenocarcinoma.

• The immunotoxin can be used in combination with standard chemotherapy.

Advantages:

• Immunotoxins are highly selective for cancer cells, reducing side-effects due to the non-specific killing of normal cells.

• Strong synergy has been shown between SS1P and standard front line cancer therapies in the treatment on lung adenocarcinoma.

• Less immunogenic PE variants increase the efficacy of the immunotoxin.

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

Patent Status: U.S. Patent 7,081,518, entitled ''Anti-mesothelin antibodies having high binding affinity'' issued on 25 July 2006 [HHS Ref. E–139–1999/0].

Related Technologies:

• U.S. Patents 6,051,405, 5,863,745, and 5,696,237 ''Recombinant Antibody-Toxin Fusion Protein'' [HHS Ref. E–135–1989/0];

• U.S. Patents 5,747,654, 6,147,203, and 6,558,672 entitled ''Recombinant Disulfide-Stabilized Polypeptide Fragments Having Binding Specificity'' [HHS Ref. E–163–1993/0];

• U.S. Patent 6,153,430, and U.S. Patent Application 09/684,599 ''Nucleic Acid Encoding Mesothelin, a Differentiation Antigen Present on Mesothelium, Mesotheliomas and Ovarian Cancers'' [HHS Ref. E–002–1996/0];

• U.S. Patent 6,083,502 entitled ''Mesothelium Antigen and Methods and Kits for Targeting It'' [HHS Ref. E–002–1996/1];

• U.S. Patent Application 09/581,345: ''Antibodies, Including Fv Molecules, and Immunoconjugates Having High Binding Affinity for Mesothelin and Methods for Their Use'' [HHS Ref. E–021–1998/0];

• U.S. Patent Application 10/297,337, ''Pegylation of Linkers Improves Antitumor Activity and Reduces Toxicity of Immunoconjugates'' [HHS Ref. E–216–2000/2];

• U.S. Patent Application 11/920,222 entitled ''Anti-Mesothelin Antibodies Useful For Immunological Assays'' [HHS Ref. E–015–2005/0];

• U.S. Patent Application 11/997,202 ''Mutated Pseudomonas Exotoxins with Reduced Antigenicity'' [HHS Ref E–262–2005/0]; and

• U.S. Patent Application 60/969,929 ''Deletions in Domain II of Pseudomonas Exotoxin A that Remove Immunogenic Epitopes without Affecting Cytotoxic Activity'' [HHS Ref. E–292–2007/0].

Licensing Status: The technology is available for exclusive and non-exclusive licensing.

Licensing Contact: David A. Lambertson, PhD; 301–435–4632; *lambertsond@mail.nih.gov*.

Collaborative Research Opportunity: The National Cancer Institute Laboratory of Molecular Biology is seeking statements of capability or interest from parties interested in collaborative research to further develop immunotoxin SS1P. Please contact John D. Hewes, PhD at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

Dated: September 9, 2008.

Richard U. Rodriguez,

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

[FR Doc. E8–21506 Filed 9–15–08; 8:45 am]

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Compositions and Methods for Increasing Recombinant Protein Yields Through the Modification of Cellular Properties

Description of Technology: This technology relates to compositions and methods for improving the growth characteristics of cells engineered to produce biologically active products such as antibodies or glycosylated proteins. Featured is a method that uses gene candidates (e.g., cdkl3, siat7e, or lama4), or their expressed or inhibited products in cell lines, such as Human Embryonic Kidney (including HEK–293), HeLa, or Chinese Hamster Ovary (CHO). The gene expression modulates growth characteristics, such as adhesion properties, of the cell lines thereby increasing recombinant protein yields and reducing product production costs.

Applications: This technology may be used to improve production of therapeutic and/or diagnostic compounds, including therapeutic proteins or monoclonal antibodies from mammalian cells. Optimization of mammalian cells for use as expression systems in the production of biologically active products is very difficult. For certain applications, anchorage-independent cell lines may be preferred, whereas for other applications, a cell line that adheres to a surface, e.g., is anchorage-dependent, may be preferable. This technology provides a method for identifying a gene whose expression modulates such cellular adhesion characteristics. This method thus leads to an increase in the expression or yield of polypeptides, including therapeutic biologicals, such as antibodies, cytokines, growth factors, enzymes, immunomodulators, thrombolytics, glycosylated proteins, secreted proteins, and DNA sequences encoding such polypeptides and a reduction in the associated costs of such biological products.

Advantages: This technology offers the ability to improve yields and reduce the cost associated with the production of recombinant protein products through the selection of cell lines having:

• Altered growth characteristics.
• Altered adhesion characteristics.
• Altered rate of proliferation.
• Improvement in cell density growth.
• Improvement in recombinant protein expression level.

Market: Biopharmaceuticals, including recombinant therapeutic proteins and monoclonal antibody-based products used for in vivo medical purposes and nucleic acid based medicinal products now represent approximately one in every four new pharmaceuticals on the market. The market size has been estimated at $33 billion in 2004 and is projected to reach $70 billion by the end of the decade. The list of approved biopharmaceuticals includes recombinant hormones and growth factors, mAB-based products and therapeutic enzymes as well as recombinant vaccines and nucleic acid based products.

Mammalian cells are widely used expression systems for the production of biopharmaceuticals. Human embryo kidney (including HEK–293) and Chinese hamster ovary (CHO) are host cells of choice. The genes identified in this technology (e.g., cdkl3, sia7e, or lama4) can be used to modify these important cell based systems.

This technology is ready for use in drug/vaccine discovery, production and development. The technology provides methods for identification of specific gene targets useful for altering the production properties of either existing cell lines to improve yields or with new cell lines for the production of therapeutic and/or diagnostic compounds from mammalian cells.

Companies that are actively seeking production platforms based on mammalian cell lines that offer high