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.

Selenocysteine Mediated Hybrid Antibody Molecules

Description of Technology: Available for licensing is a new class of hybrid molecules composed of an antibody, or antibody fragment, and a small synthetic molecule (such as a small molecule inhibitor, or cytotoxic compound). These biological and chemical components are covalently linked at an engineered selenocysteine near the C-terminus of the antibody, or antibody fragment. Through this covalent linkage, the chemical and the biological component can acquire properties of one another. For example, the synthetic molecule acquires antibody properties such as circulatory half-life, effector functions, and ability to interfere with protein interactions whereas the antibody, or antibody fragment, acquires properties of the small synthetic molecule such as specificity, affinity, and stability to bind to targets that are sterically inaccessible to immunoglobulins. The technology can also be used to equip an antibody, or antibody fragment, with a small synthetic molecule that enhances target destruction or imaging capabilities through site-selective biotinylation, PEGylation, addition of an imaging agent, or addition of a cytotoxic agent such as a chemotherapeutic drug or a chelate for radioisotope labeling. The hybrid antibody molecules can be engineered with a variety of small synthetic molecules, and the combination of immunogenic properties and those of the small synthetic molecules results in compounds with powerful target destruction or imaging capabilities. This technology could be applied towards the targeted delivery of small synthetic molecules to various cell surface receptors, and may have applicability as a prevention, diagnosis, or therapy for numerous disease states.

Applications: Potent novel compositions that retains immunogenic properties and those of small synthetic molecules that can be produced at a large scale; Method to prevent, diagnose, and treat cancer, infectious diseases and autoimmune diseases.

Market: Monoclonal antibody market is projected to exceed $30 billion by 2010; Revenue from antibodies for therapeutics and diagnostic uses are expected to grow at an average annual growth rate of 11.5%.

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

Inventors: Christoph Rader *et al.* (NCI).

Patent Status: U.S. Provisional Application No. 60/909,665 filed 02 Apr 2007 (HHS Reference No. E–146–2007/0–US–01).

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

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

Collaborative Research Opportunity: The National Cancer Institute, 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 Selenocysteine Mediated Hybrid Antibody Molecules. Please contact Dr. Christoph Rader at (301) 451–2235 or *raderc@mail.nih.gov* for more information.

Mutant Alleles of Hsp90 that Modulates the Lifespan of Yeast

Description of Technology: Heat shock protein 90 (Hsp90) are a class of chaperone proteins that are up-regulated in response to elevated temperature and other environmental stresses. They act as chaperones to other cellular proteins and facilitate their proper folding and repair, and aid in the refolding of misfolded client proteins.

This invention identifies Hsp90 mutant residues that affect the chronological lifespan of yeast. These mutations in addition to a deletion in the sch9 allele, the yeast homolog to human kinase AKT, can increase yeast lifespan from 45 to 57 days, approximately 20% longer than the wildtype strain. These genetically engineered yeast strains may have the longest chronological lifespan reported to date.

Applications: Model to study aging and longevity factors; Model to screen compounds that affect lifespan; A long-lived yeast strain could be used to ferment alcohol in a more efficient and cost effective as an alternative fuel source; Method to extend lifespan of transgenic farm animals.

Market: Anti-aging and alternative fuel industries are worth billions of dollars.

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

Inventors: Bradley T. Scroggins (NCI) *et al.*

Related Publication: BT Scroggins et al. An acetylation site in the middle domain of Hsp90 regulates chaperone function. Mol Cell. 2007 Jan 12;25(1):151–159.

Patent Status: U.S. Provisional Application No. 60/848,346 filed 09 Sep 2006 (HHS Reference No. E–319–2006/0–US–01).

Licensing Status: Available for non-exclusive licensing.

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

Collaborative Research Opportunity: The National Cancer Institute's Urologic Oncology Branch is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize models to study aging and longevity factors. Please contact John D. Hewes, Ph.D. at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

Inhibitors of Ubiquitin E1

Description of Technology: The present invention discloses novel pyrazolidinyl compounds that inhibit undesired cell proliferation. The compounds inhibit ubiquitin E1 and can be useful for regulating protein ubiquitination. Specifically, the novel pyrazolidinyl compounds can stabilize p53 and induce apoptosis in mammalian cells through selective inhibition of ubiquitin E1.

Ubiquitin-mediated proteolysis is an important pathway of non-lysosomal protein degradation that controls the timed destruction of a number of cellular regulatory proteins including p53. The ubiquitin pathway leads to the

covalent attachment of poly-ubiquitin chains to target substrates which are then degraded by a multi-catalytic proteosome complex.

The compounds can be useful in the treatment of solid and disseminated cancers or other undesired cell proliferation disease or retroviral infections such as HIV.

Applications and Modality: Treatment of disorders related to ubiquitin E1, such as HIV and viral infections; Compounds are the first general inhibitors of Ubiquitin E1 with broader biological effects than existing proteosome inhibitors; The compounds can serve as a probe to understand the ubiquitin system.

Market: Bortezomib (marketed as Velcade™ by Millennium Pharmaceuticals) is the first therapeutic proteasome inhibitor approved by the FDA. Severe side effects such as peripheral neuropathy occur in 30% of patients treated with Bortezomib. New drugs targeting proteins in ubiquitination pathway are needed that will have broader efficacy and reduced side effects.

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

Inventors: Allan M. Weissman *et al.* (NCI).

Related Publications:

1. A manuscript related to this technology will be available as soon as it is accepted for publication.

2. Y Yang et al. Small molecule inhibitors of HDM2 ubiquitin ligase activity stabilize and activate p53 in cells. Cancer Cell. 2005 Jun;7(6):547–559.

Patent Status: U.S. Provisional Application No. 60/738,242 filed 19 Nov 2005, entitled ''Inhibitors of Ubiquitin E1'' (HHS Reference No. E–070–2005/0–US–01); International Patent Application No. PCT/US2006/0045032 filed 20 Nov 2006, entitled ''Inhibitors of Ubiquitin E1'' (HHS Reference No. E–070–2005/0–PCT–02)

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

Licensing Contact: Thomas P. Clouse; 301/435–4076; *clousetp@mail.nih.gov*.

Collaborative Research Opportunity: The National Cancer Institute's Laboratory of Protein Dynamics and Signaling is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize inhibitors of ubiquitin E1. Please contact John D. Hewes, Ph.D. at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

Biomarkers for Tissue Status

Description of Technology: Tissue regeneration and tumorigenesis are complex, adaptive processes controlled by cues from the tissue microenvironment. There are complex processes both characterized by cell proliferation, migration, and angiogenesis suggesting that wounds and cancer share a number of phenotypic similarities including cellular behavior, signaling molecules, and gene expression.

Utilizing the kidneys as a model to compare renal regeneration and repair (RRR) from ischemically-injured tissues and renal cellular carcinoma (RCC), the inventors have identified biomarkers which are differentially expressed. The invention relates to methods of quickly and accurately diagnosing RCC and monitoring renal tissue health as well as RCC treatment.

Applications: Method to accurately diagnose RCC; RCC biomarker inhibitors such siRNA; Method to treat RCC; Method to determine and monitor renal tissue health status; Method for improving renal ischemia recovery without promoting RCC; Biomarkers for immunotherapy, drug targeting and drug screening, for targeting tumors and not normal regenerating tissue; Biomarkers for immunotherapy, drug targeting and drug screening, for targeting ischemic tissue and not tumors.

Market: Kidney cancer is one of the top ten most prevalent cancers in the U.S. and it accounts for 12,200 deaths annually; Approximately 35,000 new cases of kidney cancer are diagnosed annually; 50% survival rate after five years of diagnosis; Renal cancer accounts for 3% of all adult male malignancies.

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

Inventors: Joseph Riss (NCI) *et al.*

Publications:

1. Journal of Urology, May 2007, Vol. 177 No. 5, in press.

2. J Riss et al. Cancers as wounds that do not heal: differences and similarities between renal regeneration/repair and renal cell carcinoma. Cancer Res. 2006 July 15;66(14):7216–7224.

Patent Status: U.S. Provisional Application No. 60/649,208 filed 01 Feb 2005 (HHS Reference No. E–064–2005/0–US–01); PCT Application No. PCT/US2006/003611 filed 01 Feb 2006 (HHS Reference No. E–064–2005/0–PCT–02).

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

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

Collaborative Research Opportunity: The National Cancer Institute, Center for Cancer Research, Laboratory of Cancer Biology and Genetics, Wound Healing and Oncogenesis (NCI/CCR/LCBG), is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize topics of invention or related to cancer biology, metastasis, wound healing, bioinformatics, pharmacogenomics and therapeutic. Please contact John D. Hewes, Ph.D. at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

New Maleiimide Anti-Phosphatase Inhibitors

Description of Technology: The present invention describes novel phenyl maleiimide phosphatase inhibitors that appear to target the Cdc25 family of phosphatases. The new compounds are inhibitors of several human tumor cell lines. The compounds have potent activity against human liver cancer cells in vitro and in vivo against an orthotopic liver cancer in rats. In tumor cells, these new inhibitors appear to target the phosphorylation status of several cell cycle proteins that are important for cell survival and thus could represent a novel class of chemotherapeutic agents targeting cancer cells.

Applications and Modality: Compound targets Cdc25 family of phosphatases and inhibit growth of several human tumor cell lines; Potent activity in vitro against human liver cancer cells and in vivo against orthotopic liver cancer in rats; Targets phosphorylation of cell cycle proteins important for cell survival.

Market: 600,000 deaths from cancer related diseases were estimated in 2006; In 2006, cancer drug sales were estimated to be $25 billion.

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

Inventors: Christopher Michejda (NCI) *et al.*

Relevant Publication: S Kar, M Wang, W Yao, CJ Michejda, BI Carr. PM–20, A novel inhibitor of Cdc25A, induces extracellular signal-regulated kinase 1/2 phosphorylation and inhibits hepatocellular carcinoma growth in vitro and in vivo. Mol Cancer Ther. 2006 Jun;5(6):1511–1519.

Patent Status: PCT Patent Application No. PCT/US2005/05742 filed 22 Feb 2005, which published as WO 2005/081972 on 09 Sep 2005 (HHS Reference No. E–110–2004/0–PCT–02); U.S. Patent Application No. 11/508,605 filed 22

Aug 2006 (HHS Ref. No. E–110–2004/0–US–06).

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

Licensing Contact: Adaku Nwachukwu, J.D.; 301/435–5560; *madua@mail.nih.gov*.

Leu574 of HIF–1alpha as a Molecular Basis for Therapeutic Application

Description of Technology: The hypoxia-inducible factor 1 (HIF–1) is a transcription factor that plays a pivotal role in cellular adaptation to oxygen availability. HIF–1alpha protein is a subunit of HIF–1. Although the gene for HIF–1alpha is constitutively expressed, it is an extremely short-lived protein under normoxic conditions and is targeted for destruction via the proteosome pathway by an E3 ubiquitin ligase involving the VHL protein.

The invention relates to the discovery that mutations or deletions of Leu574 result in a more stable and more active form of HIF–1alpha. Therefore, the invention relates to methods and compositions for modulating oxygen homeostasis for therapeutic application. In one aspect, the inventors contemplate the use of a more stable form of HIF–1alpha protein for therapeutic angiogenesis purposes such as may be useful in ischemic vascular disease. In another aspect, the inventors contemplate the use of this particular site in a screen for targeted drugs that modulates HIF–1alpha activity. The inventors also suggest that Leu574 could be used for developing drugs targeted to HIF hydroxylase binding, thereby altering HIF–1alpha stability.

Inventor: L. Eric Huang (NCI).

Patent Status: U.S. Patent No. 7,193,053 issued 20 Mar 2007 (HHS Reference No. E–281–2002/0–US–02).

Licensing Status: This technology is available for licensing on an exclusive or a non-exclusive basis.

Licensing Contact: Jesse S. Kindra, J.D.; 301/435–5559; *kindraj@mail.nih.gov*.

Dated: April 30, 3007.

Steven M. Ferguson,

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

[FR Doc. E7–8893 Filed 5–8–07; 8:45 am]

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.

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.

New Compounds and Methods for the Treatment of Spinal Muscular Atrophy and Other Diseases

Description of Technology: Spinal muscular atrophy (SMA) is caused by mutations in the *SMN1* gene that result in reduced expression of the survival motor neuron (SMN) protein and a loss of spinal motor neurons. An *SMN2* gene paralog that differs from SMN by a single base pair has inadequate expression of SMN to support motor neuron survival. Alternative splicing caused by the single base substitution in the *SMN2* gene results in a slightly truncated and highly unstable SMN protein. Drugs that allow translational read through of the stop codons introduced by the alternative splice event have been shown to stabilize the mutant protein, resulting in increased levels of SMN.

A chemical library screen identified indoprofen, a nonsteroidal anti-inflammatory drug, as an inducer of SMN expression in cultured cells. However, indoprofen cannot enter the brain in satisfactory amounts, has a relatively low level of activity and can cause substantial side-effects in part due to its cyclooxygenase inhibitory activity. NIH inventors designed indoprofen derivatives without cyclooxygenase activity that can enter the CNS and increase expression of a SMN protein from the *SMN2* gene with increased potency and efficacy. The mechanism of action of these indoprofen analogs appears to be translational readthrough of stop codons introduced by the alternative *SMN2* splicing event. In addition to treating SMA, novel drugs that allow read through of stop codons could potentially treat many other diseases caused by such mutations such as cystic fibrosis and muscular dystrophy.

Available for licensing are compounds and methods useful for the treatment of spinal muscular atrophy by increasing SMN expression and increasing the expression from any nucleic acid that encodes a translational stop codon.

Applications: Efficacious treatment for SMA, utilizing indoprofen analogs that increase SMN protein expression; Treatment of any genetic disease caused by premature termination of protein translation.

Market: SMA is a rare genetic disease that affects approximately 1 in 6,000 live births, and is the leading genetic cause of death in infants and toddlers. The projected market size for SMA is between $250 million and $750 million.

Development Status: Clinical candidate selection scheduled for June 2007.

Inventors: Jill Heemskerk (NINDS), et al.

Publication: MR Lunn, DE Root, AM Martino, SP Flaherty, BP Kelley, DD Coovert, AH Burghes, NT Man, GE Morris, J Zhou, EJ Androphy, CJ Sumner, BR Stockwell. Indoprofen upregulates the survival motor neuron protein through a cyclooxygenase-independent mechanism. Chem. Biol. 2004 Nov;11(11):1489–1493.

Patent Status: U.S. Provisional Application No. 60/783,292 filed 17 Mar 2006 (HHS Reference No. E–133–2006/0-US–01); PCT Application No. PCT/2007/006772 filed 16 Mar 2007 (HHS Reference No. E–133–2006/1–PCT–01)

Licensing Availability: Available for exclusive and non-exclusive licensing.

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

STAMP, a Novel Cofactor and Possible Steroid Sparing Agent, Modulates Steroid-Induced Induction or Repression of Steroid Receptors

Description of Technology: Steroid hormones such as androgens, glucocorticoids, and estrogens are used in the treatments of many diseases. They act to regulate many physiological responses by binding to steroid