Dated: January 14, 2005.

Dr. Carl Roth,

Associate Director for Scientific Program Operations, National Heart, Lung, and Blood Institute.

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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.

Treatment of Inappropriate Immune Responses

Drs. He Xu and Allan D. Kirk (NIDDK)
U.S. Provisional Patent Application filed Jun 18, 2004 (DHHS Reference No. E–102–2004/0–US–01)
Licensing Contact: Marlene Shinn-Astor; 301/435–4426; *shinnm@mail.nih.gov.*

Activated human leukocytes play an essential role in counter-adaptive immune responses such as allograft rejection, autoimmune disease, and graft-versus-host disease. Depletion of leukocytes involved in these responses by using preparations of leukocytes-specific antibodies may be therapeutic in preventing and reversing these conditions. To date, however, the available monoclonal preparations do not have sufficiently broad specificity to limit the activity of many types of cells involved in counter-adaptive immunity, and the available polyclonal preparations have significant side effects caused by their unintended specificity for bystander cells or cells with beneficial properties.

The NIH announces a new treatment for blocking an undesirable immune response, wherein polyclonal antibodies are designed to preferentially target activated immune cells, rather than resting immune cells or blood cells involved in non-immune processes. These antibodies have a heightened specificity for activated lymphocytes and monocytes and decreased activity for resting or beneficial leukocytes and other blood elements.

A Novel Nuclear Receptor Cofactor Modulates Glucocorticoid-Responsive Gene Expression

S. Stoney Simons and Yuanzheng He (NIDDK);
U.S. Patent Application No. 60/548, 039 filed 26 Feb 2004 (DHHS Reference No. E–056–2004/0–US–01);
Licensing Contact: Susan Carson, (301) 435–5020; *carsonsu@mail.nih.gov.*

Nuclear receptors are ligand-activated transcription factors that regulate a wide range of biological processes and dysfunction of these receptors can lead to proliferative, reproductive and metabolic diseases, such as cancer, infertility, obesity and diabetes. Nuclear receptors are the second largest class of drug targets and the market for nuclear receptor targeted drugs is estimated to be almost 15% of the $400 billion global pharmaceutical market. Researchers at the National Institute of Diabetes and Digestive and Kidney Disease have isolated a novel protein termed STAMP (SRC–1 and TIF–2 Associated Modulatory Protein) that interacts with the biologically active domains of the coactivators TIF–2 and SRC–1 (J. Biol. Chem. (2002) 51, 49256–66) and present data which support a role for STAMP as an important new factor in the glucocorticoid regulatory network. There remains a need for novel therapeutics that specifically block or enhance specific genes and an emerging therapeutic goal is the discovery of agents that modulate co-activators or co-repressors in a tissue specific manner.

The invention is a novel protein that plays a key role in modulating transcriptional properties of glucocorticoid receptor (GR)-steroid complexes during both gene induction and gene repression, and is likely to modulate the transcriptional properties of all the steroid receptors including androgen, mineralocorticoid and progesterone receptors. The inventors have shown that ectopically expressed STAMP protein both modulates the EC50 of glucocorticoid receptor-agonist complexes for induced genes and increases glucocorticoid receptor-repressive activity of suppressed genes in a manner that is inhibited by specific siRNAs under physiologically relevant conditions. The modulation of STAMP levels at the cell or organism level could possibly be used as a therapeutic able to modify inappropriate gene expression that occurs in certain diseases or as a result of long-term steroid treatment.

Available for licensing are claims directed to compositions which are capable of modulating the GR gene expression in a mammalian cell using DNA, siRNA or antibodies and to methods of shifting a steroid dose-response curve, where less of the steroid needs to be administered because the composition contains the STAMP polypeptide. The novel STAMP functional sequence can be used in a composition of matter claim or as a target that could be regulated by an antibody or perhaps other modulator that would vary the ability of STAMP to either induce or repress the activity of glucocorticoid receptors. Diseases that could be treated include: hypertension, diabetes, cardiovascular disease, osteoporosis, Cushing's Disease as well as any disease requiring chronic steroid treatment such as Rheumatoid Arthritis, Asthma, inflammatory and auto-immune diseases. The present invention provides a broad, flexible IP platform that should be of interest to companies which focus on nuclear receptors as drug target and lead discovery generators, as well as to companies which have the capability to develop STAMP's potential as a therapeutic.

In addition to licensing, the technology is available for further development through collaborative research with the inventors via a Cooperative Research and Development Agreement (CRADA).

Generation of Smad3-Null Mice and Smad4-Conditional Mice

Chuxia Deng (NIDDK);
DHHS Reference Nos. E–349–2003/0 and E–350–2003/0—Research Tools;
Licensing Contact: Marlene Shinn-Astor; (301) 435–4426; *shinnm@mail.nih.gov.*

SMADs are a novel set of mammalian proteins that act downstream of TGF-beta family ligands. These proteins can be categorized into three distinct functional sets, receptor-activated SMADs (SMADs 1, 2, 3, 5, and 8), the common mediator SMAD (SMAD 4), and inhibitory SMADs (SMADs 6 and 7). SMAD proteins are thought to play a role in vertebrate development and tumorigenesis.

One of the research tools our NIH inventors have prepared is the Smad3-null mice model, created by disrupting exon 8 on the *Smad3* gene. Symptomatic mice exhibit leukocytosis, with massive inflammation and pyogenous abscess formation adjacent to mucosal surfaces. Smad3 plays an important role in mediating TGF-beta signals in T lymphocytes and in neutrophils, and demonstrate that Smad3 deficiency results in immune dysregulation and susceptibility to opportunistic infection, ultimately leading to the lethality of the mice between 1 and 8 months. TGF-beta signals also play a role in cancer formation in multiple organs and tissues. Smad3-null mice could be used to clone downstream target genes for TGF-beta signals, which may be used in gene therapy and chemoprevention studies.

Smad4-null mice die around embryonic day 6.5, so the inventors prepared the SMAD4-conditional mice model, created by a *Smad4* conditional knockout allele at exon 8 using Cre-mediated recombination. PCR analysis determined Cre-mediated recombination in the pancreas but not in a number of other organs, indicating that the *Smad4* conditional allele can be recombined to delete exon 8 in a tissue-specific fashion. This knockout mouse could be used to test the function of TGF-beta/Smad4 signals at all stages of mouse development. Interestingly, mutation of human *Smad4* has been found in approximately half of all pancreatic cancers, 30 percent of colon cancers, and about 10 percent in other cancers. The Smad4-conditional mice could be used to study pathways that are involved in formation of these tumors or to clone downstream target genes that may be used in gene therapy and chemoprevention studies.

Additional information may be found in the following research articles: Yang *et al.*, ''Generation of Smad4/Dpc4 conditional knockout mice,'' Genesis 2002 Feb; 32(2):80–81, Epub 13 Feb 2002 doi 10.1002/gene.10029; Yang *et al.*, ''Targeted disruption of SMAD3 results in impaired mucosal immunity and diminished T cell responsiveness to TGF-beta,'' EMBO J. 1999 Mar 1; 18(5):1280–1291, Epub doi: 10.1093/emboj/18.5.1280.

In addition to licensing, the technology is available for further development through collaborative research with the inventors via a Cooperative Research and Development Agreement (CRADA).

Anti-Proliferative Activity of an Unexpected mTOR Kinase Inhibitor

Joel Moss and Arnold Kristof (NHLBI);
U.S. Provisional Patent Application No. 60/528,340 filed 09 Dec 2003 (DHHS Reference No. E–259–2003/0–US–01); PCT Application filed 09 Dec 2004 (DHHS Reference No. E–259–2003/0–PCT–02);
Licensing Contact: Susan Carson; 301/435–5020; *carsonsu@mail.nih.gov.*

The second leading cause of death in the United States is cancer and more than one million Americans are diagnosed with cancer each year, with this number likely to increase as the population ages. There remains a need for effective therapeutics with improved safety profiles, and promising results have been obtained from targeting the phosphatidylinositol-3-kinase (PI3K) signalling cascade (including PI3K, AKT/PKB and mammalian target of rapamycin (mTOR/S6K) kinases) which is integral to the regulation of cell growth, protein synthesis and apoptosis in response to nutrients and mitogens, and which is frequently dysregulated in different cancers and other proliferative diseases. In particular, efforts have been directed at inhibiting specific kinases in this pathway as effective treatments for cancer, restenosis and autoimmune diseases and researchers at the National Heart, Lung and Blood Institute have recently shown that one of the 4H-1-benzopyran-4—one derivatives is unexpectedly an effective mTOR inhibitor.

Proof of concept data is available. This compound has been shown to attenuate tumor growth in an in vivo human xenograft PC–3 prostate tumor model, without observed toxicity. An improved therapeutic safety profile is suggested, as this compound was a weak inhibitor of PI3K. Further data indicate that inhibition of cell proliferation occurs through both mTOR-dependent and mTOR-independent mechanisms, suggesting a novel kinase inhibitor. Additionally, this cytostatic compound is shown to have an anti-inflammatory effect in peritoneal macrophages. Finally, this compound inhibits primary human smooth muscle cell proliferation in vitro, suggesting a possible role in the treatment of vascular restenosis.

This compound may therefore prove to be an effective anti-proliferative therapeutic. Available for licensing are methods of use directed to derivatives of 2-(4-piperazinyl)-substituted 4H-1-benzopyran-4—one compounds as antiproliferative, immunosuppressive and anti-neoplastic agents.

In addition to licensing, the technology is available for further development through collaborative research with the inventors via a Cooperative Research and Development Agreement (CRADA contact: Vincent Kolesnitchenko; Tel: (301) 402–5579; E-mail: kolesniv@nhlbi.nih.gov).

Methods for Making and Using Mass Tag Standards for Quantitative Proteomics

David E. Anderson (NIDDK);
U.S. Provisional Application No. 60/574,612 filed 25 May 2004 (DHHS Reference No. E–200–2003/0–US–01);
Licensing Contact: Fatima Sayyid; (301) 435–4521; *sayyidf@mail.nih.gov.*

There is a growing need for peptide standards for quantitative proteomic analysis of gene and cellular functions in cells and tissues. Current methods for generating peptide standards for identification and absolute quantification of proteins rely almost solely on synthetic approaches which require expensive reagents, equipment and rare expertise.

The present invention describes a process for simultaneously generating peptide standards of known concentration for several proteins of interest within a single easily parallelized experiment. This process uses a combination of automated synthetic gene design, gene synthesis, cloning, bacterial expression with heavy isotope incorporation, generic protein purification, optical quantitation, and endoprotease cleavage to make sets of peptides of known concentration. Non-modified peptides can be made for a fraction of the cost of synthetic approaches. Since the main cost involves the initial production of a DNA construct, follow-up preparations of peptides (which can use different isotope backgrounds) are even cheaper.

A Method of Treating Inflammatory Bowel Disease (IBD)

Warren Strober, Ivan Fuss, Frank Heller, Richard Blumberg (NIAID); PCT Application No. PCT/US2002/018790 filed 14 Jun 2002, which published as International Publication No. WO 2004/001655 on 31 Dec 2003 (DHHS Reference No. E–131–2002/0–PCT–01)
Licensing Contact: Susan Carson; (301) 435–5020; *carsonsu@mail.nih.gov.*

Ulcerative colitis (UC) is a chronic inflammatory disease of the colorectum and affects approximately 400,000 people in the United States (of these, approximately 5 percent develop colon cancer). The cause of UC is not known, although an abnormal mucosal T cell, responsive to bacterial antigens in the gut microflora, is thought to be

involved. Present treatments for UC include anti-inflammatory therapy using aminosalicylates or corticosteroids, as well as immunomodulators and diet. However, 25–40 percent of ulcerative colitis patients must eventually have their colons removed due to massive bleeding, severe illness, rupture of the colon, risk of cancer or due to side effects of corticosteroids and novel treatments are still actively being sought. NIH scientists and their collaborators have used a mouse model of experimental colitis (OC) to show that IL–13, a Th2 cytokine, is a significant pathologic factor in OC and that neutralizing IL–13 in these animals effectively prevents colitis (Immunity (2002) 17, 629–638).

OC is a colitis induced by intrarectal administration of a relatively low dose of the haptenating agent oxazolone subsequent to skin sensitization with oxazolone. A highly reproducible and chronic colonic inflammation is obtained that is histologically similar to human ulcerative colitis. Studies show that NKT cells rather than conventional CD4+T cells mediate oxazolone colitis and that NKT cells are the source of IL–13, and are activated by CD1 expressing intestinal epithelial cells. Tissue removed from UC patients were also shown to contain increased numbers of nonclassical NKT cells that produce markedly increased amounts of IL–13 and that in keeping with epithelial damage being a key factor in UC, these NKT cells are cytotoxic for epithelial cells (J. Clin. Investigation (2004) 113, 1490–1497).

With obvious implications for the treatment of human Ulcerative Colitis, inflammation in this mouse model has been shown to be effectively blocked by neutralizing IL–13 or by inhibiting the activation of NK–T cells through CD1. Available for licensing are broad claims covering treatments preventing the inflammatory response of colitis by modulating IL–13 and NKT cell activity and methods for screening for therapeutic compounds effective for colitis.

In addition to licensing, the technology is available for further development through collaborative research with the inventors via a Cooperative Research and Development Agreement (CRADA).

Dated: January 18, 2005.

Steven M. Ferguson,

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

[FR Doc. 05–1415 Filed 1–25–05; 8:45 am]

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Null Mutation of the CCAAT/Enhancer Binding Protein Delta (Cebpd) Gene in Mice

G. Esta Sterneck *et al.* (NCI);
DHHS Reference No. E–032–2005/0—Research Tool;
Licensing Contact: John Stansberry; 301/435–5236; *stansbej@mail.nih.gov.*

The invention describes mice with a deletion of the C/EBPdelta gene and cell lines derived from such mice. C/EBPdelta (CCAAT/enhancer binding protein delta) is implicated in the acute phase inflammatory response, long-term memory, fat cell and osteoblast differentiation, ovarian hormone responses, mammary gland involution and cell death. C/EBPdelta may also be a tumor suppressor. Fibroblasts lacking C/EBPdelta exhibit transformed features such as impaired contact inhibition, reduced serum dependence and chromosomal instability. The mice and cell lines of the invention could be useful for the study of the function of C/EBPdelta such as its potential role in cancer, and to investigate how drug responses are modified in the absence of C/EBPdelta.

In addition to licensing, the technology is available for further development through collaborative research with the inventors via a Cooperative Research and Development Agreement (CRADA).

Active Chromatin Domains Are Defined by Acetylation Islands Revealed by Genome-Wide Mapping

Drs. Keji Zhao and Tae-Young Roh (NHLBI);
U.S. Provisional Application No. 60/619,430 filed 15 Oct 2004 (DHHS Reference No. E–008–2005/0–US–01);
Licensing Contact: John Stansberry; 301/435–5236; *stansbej@mail.nih.gov.*

Epigenetics play a critical role in cellular development and cellular transformation in many pathogenic processes. For example, many cancers are correlated with changes of their chromatin structure and are sensitive to drugs that module the levels of histone acetylation. Epigenetic regulation refers to the modification of histones, which does not involve changes of DNA sequences of target genes. The present technology maps the genome-wide distribution of histone H3 acetylation in human T cells and describes over 40,000 acetylation islands. These acetylation islands are epigenetic markers for transcriptional regulatory elements and chromatin-controlling elements. Changes in acetylation islands may be correlated with early development of T cell lymphoma or leukemia. Specifically, diseases characterized by aberrant transcriptional regulation could be diagnosed earlier with the application of this technology.

Method of Detecting Cancer Based on Immune Reaction to BORIS

Victor Lobanenkov *et al.* (NIAID);
U.S. Provisional Application No. 60/611,798 filed 21 Sep 2004 (DHHS Reference No. E–241–2004/0–US–01);
Licensing Contact: Mojdeh Bahar; 301/435–2950; *baharm@mail.nih.gov.*

The invention provides a method of detecting autoantibodies to BORIS (brother of the regulator of imprinted sites) as a possible screen for cancer and a kit comprising BORIS peptides and epitopes. BORIS is a protein that is expressed in many cancers but not in normal tissues (except testis) and thus is a potential target for a cancer therapeutic or diagnostic.

Importantly, BORIS is a cancer-testis (CT) antigen, which despite that it is intracellular protein upon abnormal expression in cancer it appears to be immunogenic in humans. Thus, BORIS could be employed in cancer diagnosis using serum from patients. In fact, the inventors detected BORIS-specific antibodies in serum from patients with gliomas, lung, breast and prostate