advice regarding a particular drug combination development program, a sponsor should contact the appropriate review division before submitting an Investigational New Drug application. In addition, FDA is in the process of publishing more specific guidance for certain categories of drug combinations.

The guidance discusses drug combinations involving the following items: (1) Previously marketed drugs, (2) one or more new molecular entities (NMEs) and one or more previously marketed drugs, and (3) more than one NME. The nonclinical studies considered important for each type of combination may differ, depending upon the information available on each drug component (active pharmaceutical ingredient). The nonclinical studies that would be appropriate to adequately characterize the combination depend on the toxicologic and pharmacokinetic profiles of the individual drugs, the treatment indication or indications, and the intended population.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the agency's current thinking on nonclinical safety evaluation of drug combinations. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments on the draft guidance. Two copies of mailed comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments are available for public examination in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

III. Electronic Access

Persons with access to the Internet may obtain the document at either *http://www.fda.gov/cder/guidance/index.htm* or *http://www.fda.gov/ohrms/dockets/default.htm*.

Dated: January 18, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 05–1394 Filed 1–25–05; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Heart, Lung, and Blood Institute (NHLBI); Opportunity for a Cooperative Research and Development Agreement (CRADA) to Identify and Explore Epigenetic Regulatory Elements for Diagnostic and Therapeutics Purposes

AGENCY: National Institutes of Health, Public Health Service, HHS.

ACTION: Notice.

SUMMARY: The National Heart, Lung, and Blood Institute (NHLBI) is seeking Cooperative Research and Development Agreement (CRADA) collaborator(s) to work with investigators in the Laboratory of Molecular Immunology (LMI) to identify epigenetic regulatory elements that may be involved in the disease development of T and/or B cell leukemia/lymphoma and other cancers via genome-wide analysis of acetylation islands using the Genome-Wide Mapping Technique (GMAT). Representative disease-specific acetylation islands will be explored for diagnostic and therapeutic purposes.

SUPPLEMENTARY INFORMATION: 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 modulate the levels of histone acetylation. Epigenetic regulation refers to the modification of chromatin including posttranslational modification of histones, which does not involve change of DNA sequences of target genes. MHLBI investigators have mapped the genome-wide distribution of histone H3 acetylation in human T cells and discovered over 40,000 acetylation islands using a technique called GMAT. This tool combines Chromatin immunoprecipitation (Chip) of hyper-acetylated histones, with Serial Analysis of Gene Expression (SAGE). The acetylation islands are epigenetic markers for transcriptional regulatory elements and chromatin controlling elements. Changes of the acetylation islands may be correlated with early development of T cell lymphoma or leukemia. Therefore, this discovery may be applied to early diagnosis and/or treatment of these diseases.

The NHLBI is seeking capability statements from parties interested in entering into a CRADA to identify, explore and further develop epigenetic regulatory elements/acetylation islands for diagnostic and therapeutic purposes. The role of the CRADA collaborator(s) will include, but not be limited to, the following:

1. The ability to collaborate with NHLBI on further research and development of this technology. This ability can be demonstrated through experience and expertise in this or related areas of technology indicating the ability to contribute intellectually to on-going research and development.

2. To assist with obtaining specimen/tissues (patient and normal controls) for the Genome-Wide analysis as diagnostic and therapeutic markers.

3. To assist to further developing the epigenetic regulatory elements markers/acetylation islands as new targets for novel drug-development strategies.

The collaborator may also be expected to contribute financial support under this CRADA for personnel, supplies, travel, and equipment to support these projects. The collaborator is also expected to cooperate with the NHLBI in the timely publication of research results and to accept the legal provisions and language of the CRADA with only minor modifcations, if any.

DATES: CRADA capability statements should be submitted to Vincent Kolesnitchenko, Ph.D., Technology Transfer Specialist, National Heart, Lung, and Blood Institute (NHLBI), Office of Technology Transfer and Development, National Institutes of Health, 6705 Rockledge Drive, Suite 6018, MSC 7992, Bethesda, MD 20892–7992; Phone: (301) 594–4115; Fax: (301) 594–3080; E-mail: *vk5q@nih.gov*. Capability statements must be received on or before March 28, 2005.

The NHLBI has applied for patents claiming the core of the technology. Non-exclusive and/or exclusive licenses for these patents covering core aspects of this project are available to interested parties.

Licensing inquiries regarding this technology should be addressed to John Stansberry, Ph.D., Technology Licensing Specialist, Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804, Phone: (301) 435–5236; Fax: (301) 402–0220; E-mail: *stansbej@od.nih.gov*. Information about Patent Applications and pertinent information not yet publicly described an be obtained under the terms of a Confidential Disclosure Agreement.

Respondents interested in submitting a CRADA Proposal should be aware that it may be necessary to secure a license to the above-mentioned patent rights in order to commercialize products arising from a CRADA.

Dated: January 14, 2005.

Dr. Carl Roth,

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

[FR Doc. 05–1412 Filed 1–25–05; 8:45 am]

BILLING CODE 4140–01–M

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.