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).


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.


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

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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.


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 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
receptors. However, because steroid receptors are expressed in many tissues, efforts to therapeutically modify the effects of steroid hormones on a specific tissue or on a specific receptor of the steroid receptor family often cause undesirable effects in other tissues or on other receptors. STAMP (SRC−1 and TIF−2 Associated Modulatory Protein), a novel protein that acts to lower the concentration of steroid hormone needed to induce (or repress) selected target genes by regulating steroid receptor synthesis, offers a novel approach for reducing the severity of unwanted side-effects, thereby increasing the ability to use steroid hormone therapies.

Applications

1. Diseases requiring chronic steroid treatment such as rheumatoid arthritis, psoriatic arthritis, asthma, inflammatory and auto-immune diseases;
2. Diseases characterized by excess or deficiency of glucocorticoids such as obesity, diabetes, hypertension, Cushing’s Syndrome, Parkinson’s Disease, Addison’s Disease;
3. Diseases in which glucocorticoid-responsive gene expression is deranged, so deranging carbohydrate, protein or lipid metabolism;
4. Cancers responsive to androgen or estrogen, such as breast cancer or prostate cancer;
5. Therapeutic applications related to male or female hormone replacement, symptoms related to menopause, birth control, menstrual cycle/amenorrhea, fertility or endometriosis.

Advantages

1. STAMP reduces the severity of unwanted side-effects of steroid hormone therapies;
2. STAMP modulates the gene induction properties of androgen and progesterone receptors;
3. STAMP modulates both induction and repression properties of glucocorticoid receptors;
4. STAMP is inactive toward alpha and beta estrogen receptors, thyroid receptor beta, PPAR gamma 2, retinoid receptor alpha or RXR alpha;
5. The siRNAs could be useful as therapeutics.

Market: The protein, STAMP, offers a novel approach for reducing the severity of unwanted side-effects of steroid hormone therapies. Therefore, STAMP would be helpful in the treatment of diseases requiring chronic steroid treatments, those characterized by excess or deficiency of glucocorticoid response, therapies related to male or female hormone replacement or cancers responsive to androgen or estrogen.

Development Status

1. STAMP, a protein which is a novel nuclear receptor cofactor, has been identified;
2. STAMP siRNAs have been shown to change the dose response curve of endogenous glucocorticoid receptor induced genes;
3. A STAMP antibody has been prepared.

Further Research & Development Required

1. Further in-vivo studies into the role of STAMP in glucocorticoid receptor-mediated repression;
2. Further study into the activity of STAMP in androgen receptor-mediated responses;
3. Investigation into the mechanism of action of STAMP;
4. Development of STAMP knockout mouse.

Inventors: Drs. S. Stoney Simons Jr (NIDDK) and Yuanzheng He (NIDDK)


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

Licensing Contact: Dr. Susan Carson; 301/435–5020; carsons@mail.nih.gov.

Collaborative Research Opportunity: The National Institute of Diabetes, Digestive and Kidney Diseases, Laboratory of Molecular and Cellular Biology is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize this technology. Please contact Dr. Stoney Simons, Chief, Steroid Hormones Section (NIDDK) at steroids@helix.nih.gov; Tel: 301–4960–6796 for more information.

TMC1, a Deafness-Related Gene

Description of Technology: Hearing loss is a common communication disorder affecting nearly 1 in 1,000 children in the United States alone, and nearly 50% of adults by the age of eighty. Hearing loss can be caused by environmental and disease-related factors; however, hearing loss due to genetic factors accounts for approximately 50% of cases.

The NIH announces the isolation of two novel genes involved in hearing; TMC1, short for transmembrane channel-like gene 1. The inventors have discovered that dominant and recessive mutations in TMC1 underlie two forms of hereditary deafness, known as DFNA36 and DFNB7/11. TMC1 encodes a protein required for normal function of the mammalian hair cell, which plays a critical role within the hearing pathway that detects sound in the inner ear.

The invention discloses TMC1 nucleic acids, vectors, and cells. Also disclosed are methods of detecting hearing loss, or a predisposition to hearing loss, due to a mutation in TMC1, as well as methods for identifying agents that interact with the TMC1 gene in a cell. Nucleic acids and methods of use for TMC2, a gene closely related to TMC1, are also disclosed.

Applications: Development of a genetic diagnostic test for hearing loss; Development of pharmaceuticals to treat hearing loss.

Market: Hearing loss with a genetic component accounts for 50% of all cases of hearing loss.

Development Status: Early stage.

Inventors: Andrew J. Griffith et al. (NIDCD).


Patent Status

1. HHS Reference No. E–168–2001/0:
   a. U.S. Provisional Application No. 60/323,275 filed 19 Sep 2001.
   e. Foreign counterparts in Australia, Canada, Europe, and Japan.
2. HHS Reference No. E–168–2001/1:
   b. Foreign counterparts in Australia and Canada.

Licensing Status: Available for non-exclusive licensing.

Licensing Contact: Tara L. Kirby, Ph.D.; 301/435–4426; tarak@mail.nih.gov.
Collaborative Research Opportunity: The NIDCD Otolaryngology Branch is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize this technology as well as collaborate on further pre-clinical and clinical studies with the TMC2 gene mutations. Please contact Ms. Marianne Lynch at 301–402–5579 or via e-mail at lynchm@nhlbi.nih.gov for more information.


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

BILLING CODE 4140–01–P

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National Institutes of Health

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Influenza Vaccines and Antiviral Agents

Description of Technology: The subject invention offers candidate DNA vaccines to target H5N1, H1N1, H3N2 and other subtypes of influenza. These candidates are designed primarily to elicit neutralizing antibodies. The candidate vaccines express hemagglutinin (H/HA) or neuraminidase (N/NA) protein that has been codon optimized and/or modified at the protease cleavage site. The modified genes could be used in DNA vaccines, in viral vectors, recombinant proteins/particles or combination. The studies use proprietary expression systems that increase protein expression relative to commonly used alternatives. This invention potentially provides a vaccine strategy for controlling influenza epidemics, including avian flu, should it cross over to humans; the 1918 strain of flu; and seasonal flu strains. In addition, this invention is designed to lead to a combination vaccine to provide a broadly protective vaccine. The incorporation of specific cleavage site types to facilitate preparation of pseudotypes from a variety of strains is an important aspect of this invention.

In addition, HA pseudotyped lentiviral vectors are being tested to screen for neutralizing abs in patients and to screen for diagnostic and therapeutic monoclonal abs.

Applications and Advantages: Influenza vaccine for pandemic or epidemic application; Potential for combination vaccine for broad protection, removing need for seasonal strain monitoring; DNA vaccines are easy to produce and store; No risk of reversion to pathogenic strain as with live-attenuated virus vaccines.

Development Status Highlights: Phase I clinical trials planned for select candidates; DNA vaccine encoding 1918 influenza virus HA protein protects mice against lethal viral challenge; Codon optimized for expression in human cells.

Inventors: Gary J. Nabel (VRC/NIAID), Wing-pui Kong (VRC/NIAID), Zhi-yong Yang (VRC. NIAID), et al.


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

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

Enhanced, Targeted Delivery for DNA Vaccines

Description of Technology: Available for licensing from the NIH is a fusion protein for enhanced gene delivery. Exemplary proteins for achieving this improvement comprise an adenovirus serotype 5 fiber, penton base and core protein V fused to the DNA binding domain of HMG. In vitro studies have shown the effectiveness of the chimeric protein-DNA vaccine co-administration by an increase in uptake of ten to twenty fold. In particular, the plasmid with the chimeric core protein V was delivered efficiently to dendritic cells (DC) as well as 293T cells. The utilization of this chimeric protein could further enhance the immune response elicited by DNA vaccines.

Potential Applications: Improved DNA vaccine delivery and uptake.

Inventors: Gary J. Nabel and Wataru Akahata (VRC/NIAID).


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

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


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

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Cancer Institute; Notice of Meeting

Pursuant to section 10(a) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of a meeting of the National Cancer Institute Director’s Consumer Liaison Group.

The meeting will be open to the public, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should notify the Contact Person listed below in advance of the meeting.