

Identification of Subjects Likely To Benefit From Copper Treatment

Description of Technology: Menkes disease is an infantile onset X-linked recessive neurodegenerative disorder caused by deficiency or dysfunction of a copper-transporting ATPase, ATP7A. The clinical and pathologic features of this condition reflect decreased activities of enzymes that require copper as a cofactor, including dopamine- β -hydroxylase, cytochrome c oxidase and lysyl oxidase. Recent studies indicate that ATP7A normally responds to N-methyl-D-aspartate receptor activation in the brain, and an impaired response probably contributes to the neuropathology of Menkes disease. Affected infants appear healthy at birth and develop normally for 6 to 8 weeks. Subsequently, hypotonia, seizures and failure to thrive occur and death by 3 years of age is typical. Occipital horn syndrome (OHS) is also caused by mutations in the copper transporting ATPase ATP7A, although its symptoms are milder than Menkes syndrome, including occipital horns and lax skin and joints.

Treatment with daily copper injections may improve the outcome in Menkes disease if commenced within days after birth; however, newborn screening for this disorder is not available and early detection is difficult because clinical abnormalities in affected newborns are absent or subtle. Moreover, the usual biochemical markers (low serum copper and ceruloplasmin) are unreliable predictors in the neonatal period, since levels in healthy newborns are low and overlap with those in infants with Menkes disease. Although molecular diagnosis is available, its use is complicated by the diversity of mutation types and the large size of ATP7A (about 140kb). Thus, there is a need for improved methods for early detection of infants with Menkes disease or OHS in order to improve outcomes.

This technology relates to methods of identifying individuals who may benefit from treatment with copper, particularly those having Menkes disease or Occipital Horn Syndrome.

Inventor: Stephen G. Kaler (NICHD).

Publication: SG Kaler, CS Holmes, DS Goldstein, JR Tang, SC Godwin, A Donsante, CJ Liew, S Sato, N Patronas. Neonatal diagnosis and treatment of Menkes disease. *N Engl J Med.* 2008 Feb 7;358(6):605-614. [PubMed: 18256395]

Patent Status: PCT Application No. PCT/US2008/078966 filed 06 Oct 2008, which published as WO 2010/042102

on 15 Apr 2010 (HHS Reference No. E-186-2008/0-PCT-01).

Licensing Status: Available for licensing.

Licensing Contact: Fatima Sayyid, M.H.P.M.; 301-435-4521; Fatima.Sayyid@nih.hhs.gov.

Collaborative Research Opportunity: The National Institute of Child Health and Human Development, Division of Intramural Research, Molecular Medicine Program, Unit on Pediatric Genetics, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize population-based newborn screening for Menkes disease and related disorders of copper transport in order to identify subjects likely to benefit from copper injections and other treatments. Please contact Alan Hubbs, PhD at 301-594-4263 or hubbsa@mail.nih.gov for more information.

Dated: December 21, 2010.

Richard U. Rodriguez,

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.

A New Class of Antibiotics: Natural Inhibitors of Bacterial Cytoskeletal Protein FtsZ to Fight Drug-susceptible and Multi-drug Resistant Bacteria

Description of Technology: The risk of infectious diseases epidemic has been alarming in recent decades. This is not only because of the increase incident of so-called "super bugs," but also because of the scarce number of potential antibiotics in the pipeline. Currently, the need for new antibiotics is greater than ever! The present invention by the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), part of the National Institute of Health (NIH), address this urgent need. The invention is a new class of chrysophaeitin antibiotics that inhibit the growth of broad-spectrum, drug-susceptible, and drug-resistant bacteria.

Derived from the yellow algae *Chrysothrix taylori*, the inventor has extracted 8 small molecules of natural products and tested for antimicrobial activity against drug resistant bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE), as well as other drug susceptible strains. Structurally, the molecules represent a new class of antibiotic that also likely work through a distinct mechanism of action from that of current antibiotics, which is key for the further development of antibiotics that inhibit drug-resistant strains.

The bacterial cytoskeletal protein FtsZ is a GTPase and has structural homology to the eukaryotic cytoskeletal protein tubulin, but lacks significant sequence similarity. FtsZ is essential for bacterial cell division. It is responsible for Z-ring assembly in bacteria, which leads to bacterial cell division. Experiments show that the disclosed compounds are competitive inhibitors of GTP binding to FtsZ, and must bind in the GTP-binding site of FtsZ. Inhibition of FtsZ stops bacterial cell division and is a validated target for new antimicrobials. FtsZ is highly conserved among all bacteria, making it a very attractive antimicrobial target.

Applications:

- Therapeutic potential for curing bacterial infections in vivo, including for clinical and veterinary applications.
- Antiseptics in hospital settings.
- Since FtsZ is structurally similar, but does not share sequence homology to eukaryotic cytoskeletal protein tubulin, these compounds may have antitumor properties against some cancer types or cell lines.

Advantages:

- Structurally distinct antimicrobial compounds.
- Attack newly validated antibacterial targeted protein FtsZ.
- These compounds have a unique mechanism of action which inhibit FtsZ by inhibiting FtsZ GTPase activity.
- Inhibit drug-susceptible and drug-resistant bacteria.

Development Status:

- Initial isolation and chemical structural characterization using NMR spectroscopy have been conducted.
- Antimicrobial testing against MRSA, *Enterococcus faecium*, and VRE were conducted *in vitro* using a modified disk diffusion assay and microbroth liquid dilution assays.
- MIC₅₀ values were determined using a microbroth dilution assay.
- Mode of action was elucidated and Saturation Transfer Difference (STD) NMR was conducted to map the binding epitope of one of these compounds in complex with recombinant FtsZ.
- Other experiments on different areas to further characterize these compounds and their mode of action are currently ongoing.

Market: The market potential for the disclosed compounds is huge due to the very limited number of new antibiotics developed in recent decades and the increased epidemic of infectious diseases. In fact, infectious diseases are the leading cause of death worldwide. In the United States alone, more people die from MRSA than from HIV (Journal of the American Medical Association, 2007) and more than 90,000 people die each year from hospital acquired bacterial infections (Centers for Disease Control).

According to the recent report, "Antibiotics Resistance and Antibiotic Technologies: Global Markets" published in November 2009, there has been a revival in the antibiotics sector over the past few years. Although some companies are developing analogues of existing antibiotic classes and putting them into clinical trials, other start-up biotechnology companies have come up with molecules that adopt new approaches in tackling antimicrobial infections. The antibacterials market can be split into two major groups: The community market and the hospital market. The smaller hospital market is expanding more rapidly, driven by rising resistant rates, a more severely ill patient population and newer, premium-priced injectable antibiotics. Interestingly, several big pharmaceutical companies have recently made strategic decisions to expand their presence in this sector by either acquiring other companies or in-licensing new compounds.

While the number of such new molecules in the approval stages is still low, R&D pipelines are promising, and several novel classes of antibiotics are in their early stages of development. This antibacterial R&D bailout that started about 5 years ago due to tougher regulatory conditions, restrictions on the use of antibiotics and emergence of resistance to newer antibiotics within 3 years has helped create a global antimicrobial therapeutic market of \$24 billion in 2008 with 14 products recording sales of more than \$1 billion.

Inventors: Carole A. Bewley *et al.* (NIDDK).

Related Publications:

1. DJ Haydon *et al.* An inhibitor of FtsZ with potent and selective anti-staphylococcal activity. *Science*. 2008 Sept 19; 321(5896):1673–1675. [PubMed: 18801997].
2. NR Stokes *et al.* Novel inhibitors of bacterial cytokinesis identified by a cell-based antibiotic screening assay. *J Biol Chem*. 2005 Dec 2; 280(48):39709–39715. [PubMed: 16174771].
3. J Wang *et al.* Discovery of small molecule that inhibits cell division by blocking FtsZ, a novel therapeutic target of antibiotics. *J Biol Chem*. 2003 Nov 7; 278(45):4424–4428. [PubMed: 12952956].
4. P Domadia *et al.* Berberine targets assembly of Escherichia coli cell division protein FtsZ. *Biochemistry*. 2008 Mar 11; 47(10):3225–3234. [PubMed: 18275156].
5. P Domadia *et al.* Inhibition of bacterial cell division protein FtsZ by cinamaldehyde. *Biochem Pharmacol*. 2007 Sep 15; 74(6):831–840. [PubMed: 17662960].
6. S Urgaonkar *et al.* Synthesis of antimicrobial natural products targeting FtsZ: (+/-)-dichamanetin and (+/-)-2''-hydroxy-5''-benzylisouvarinol-B. *Org Lett*. 2005 Dec 8; 7(25):5609–5612. [PubMed: 16321003].

Patent Status: U.S. Provisional Application No. 61/308,911 filed 27 Feb 2010 (HHS Reference No. E-116-2010/0-US-01).

Licensing Status: Available for licensing.

Licensing Contacts:

- Uri Reichman, Ph.D., MBA; 301-435-4616; UR7a@nih.gov.
- John Stansberry, Ph.D.; 301-435-5236; stansbej@mail.nih.gov.

Collaborative Research Opportunity: The National Institute of Diabetes and Digestive and Kidney Diseases, Laboratory of Bioorganic Chemistry is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize the chrysphaentin antibiotics. Please

contact Cindy K. Fuchs at 301-451-3636 or cfuchs@mail.nih.gov for more information.

GATA-3 Reporter Plasmids for Revealing Underlying Mechanisms in Breast Cancer

Description of Technology: Scientists at the National Institutes of Health (NIH) have developed GATA-3 gene reporter plasmids that express a green fluorescent protein (GFP) or luciferase reporter protein under the control of a GATA-3 promoter. Cells expressing this plasmid will glow fluorescent green or emit light energy, respectively, if GATA-3 gene expression is activated in the cells. The reporter construct allows cells where GATA-3 gene expression is activated to be isolated and collected for further analysis or be monitored in the host environment.

GATA-3 is a transcription factor that is highly expressed in several types of cells and is a critical transcription factor for the development of particular lineages of hematopoietic cells and normal mammary luminal epithelium. GATA-3 plays a regulatory role in determining the fate of cells in the hematopoietic systems and the mammary gland. Disruption of GATA-3 expression leads to defects in the development of sub-types of lymphoid cells and luminal mammary epithelial cells. GATA-3 expression is highly associated with luminal sub-types of breast cancer, whereas expression of GATA-3 is low or undetectable in basal subtypes of breast cancer which often have a poor prognosis. Low or limited GATA-3 expression is correlated with larger tumors, increased likelihood of tumor-positive lymph nodes, and predicts an overall poorer clinical outcome compared to patients with higher mammary GATA-3 expression. Researchers believe that a better understanding of GATA-3 function and its dysregulation during the onset and progression of breast cancer will lead to new strategies in diagnosing and treating the disease.

Applications:

- Research tool to help identify factors that modify GATA-3 expression that may serve as potential therapeutic targets for developing drugs to treat breast cancer or hematologic malignancies.
- Research tool that could be utilized as an important component of a breast cancer diagnostic kit or platform to better understand the most effective treatment options for individual breast cancer patients.
- Molecular tool to better understand the mechanisms that contribute to hematopoietic and mammary cell/gland

development and differentiation in order to identify the critical stages where dysfunction can lead to the onset of breast cancer.

- Molecular biology laboratory tool for sorting breast cancer positive and negative cells so that further comparative experiments can be performed to understand the cellular properties of the two sets of cells.

Advantages:

- *Useful for in vitro and in vivo assays:* Using the GFP or luciferase expression of these reporter plasmids, researchers can identify cells expressing various levels of GATA-3 and isolate these different subsets *in vitro*. These reporter constructs can also be transfected into cells to measure GATA-3 expression levels *in vivo* in real time from hematopoietic and breast cancer models.

- *Possible identification of new targets for breast cancer therapy:* The reporter plasmids could be utilized to identify factors that serve to activate GATA-3 in normal mammary cells or inhibit GATA-3 expression in breast cancer cells. Such factors could serve as targets for novel breast cancer therapies.

Inventors: Hosein Kouros-Mehr (formerly NCI) and Jeffrey E. Green (NCI)

Selected Publications:

1. H. Kouros-Mehr, *et al.* GATA-3 and the regulation of the mammary luminal cell fate. *Curr Opin Cell Biol.* 2008 Apr;20(2):164-170. [PubMed: 18358709]

2. H. Kouros-Mehr, *et al.* GATA-3 links tumor differentiation and dissemination in the luminal breast cancer model. *Cancer Cell* 2008 Feb;13(2):141-152. [PubMed: 18242514]

3. H. Kouros-Mehr, *et al.* GATA-3 maintains the differentiation of the luminal cell fate in the mammary gland. *Cell* 2006 Dec 1;127(5):1041-1055. [PubMed: 17129787]

Patent Status: HHS Reference No. E-128-2009/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Status: Available for licensing under a Biological Materials License Agreement.

Licensing Contact: Samuel E. Bish, Ph.D.; 301-435-5282; bishse@mail.nih.gov.

Dated: December 21, 2010.

Richard U. Rodriguez,

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

[FR Doc. 2010-32671 Filed 12-27-10; 8:45 am]

BILLING CODE 4140-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Biomedical Imaging and Bioengineering; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. App.), notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute of Biomedical Imaging and Bioengineering Special Emphasis Panel.

Date: March 16-18, 2011.

Time: 6 p.m. to 3 p.m.

Agenda: To review and evaluate grant applications.

Place: Sheraton Fisherman's Wharf Hotel, 2500 Mason Street, San Francisco, CA 94133.

Contact Person: Ruth Grossman, DDS, Scientific Review Officer, National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health, 6707 Democracy Boulevard, Room 960, Bethesda, MD 20892, 301-496-8775, grossmanrs@mail.nih.gov.

Dated: December 16, 2010.

Jennifer Spaeth,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 2010-32645 Filed 12-27-10; 8:45 am]

BILLING CODE 4140-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Center for Scientific Review; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. App.), notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning

individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: Center for Scientific Review Special Emphasis Panel; Member Conflict: Cardiac Development.

Date: January 4, 2011.

Time: 3 p.m. to 4 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892. (Telephone Conference Call).

Contact Person: Joseph Thomas Peterson, PhD, Scientific Review Officer, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 4118, MSC 7814, Bethesda, MD 20892. 301-443-8130.

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

(Catalogue of Federal Domestic Assistance Program Nos. 93.306, Comparative Medicine; 93.333, Clinical Research, 93.306, 93.333, 93.337, 93.393-93.396, 93.837-93.844, 93.846-93.878, 93.892, 93.893, National Institutes of Health, HHS)

Dated: December 21, 2010.

Jennifer S. Spaeth,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 2010-32639 Filed 12-27-10; 8:45 am]

BILLING CODE 4140-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Center for Scientific Review; Amended Notice of Meeting

Notice is hereby given of a change in the meeting of the Center for Scientific Review Special Emphasis Panel, January 6, 2011, 1 p.m. to January 6, 2011, 3:30 p.m., National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892 which was published in the **Federal Register** on December 16, 2010, 75 FR 78719-78720.

The meeting has been changed to an Internet Assisted Meeting (IAM). The meeting will be two days January 6, 2011, 9 a.m. to January 7, 2011, 5 p.m. The meeting is closed to the public.

Dated: December 21, 2010.

Jennifer S. Spaeth,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 2010-32638 Filed 12-27-10; 8:45 am]

BILLING CODE 4140-01-P