



TSC ALERT

Edited by Vicky Holets Whittemore, Ph.D. & Cheryl Dunigan, Ph.D.

May 2004

Welcome to the May 2004 edition of *TSC Alert* – an online research newsletter for individuals interested in Tuberous Sclerosis Complex (TSC) research and clinical care. This online newsletter contains information of interest to the TSC research and health care community. Please forward this newsletter to colleagues who are interested in TSC. To be added/deleted to/from the mailing list for *TSC Alert* and/or to submit information for the June 2004 *TSC Alert* contact: Vicky.Whittemore@tsalliance.org

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IMPORTANT DEADLINES:

August 1, 2004: Submission of poster abstracts for late breaking research will be accepted until August 1st 2004.

'TSC genes - function and dysfunction - from molecular biology to therapeutic advances'

September 16-18, 2004

Queens' College
University of Cambridge
Cambridge, UK

Chairmen: Professor Patrick Bolton & Dr John Yates
Sponsored by the Tuberous Sclerosis Association

Pivotal roles for the TSC genes in cell biology have come from new research since 2001. In turn, this knowledge has increased understanding of the clinical manifestations of Tuberous Sclerosis. The 2004 conference will present new research around two main themes 'Normal function of TSC genes' and 'Clinical dysfunction caused by TSC gene mutations'. There will be plenary sessions on each theme, poster presentations and an opportunity to talk about any late breaking research.

For more information, visit the Tuberous Sclerosis Association Web site: <http://www.tuberous-sclerosis.org/research/conference/index.shtml>

GRANT ANNOUNCEMENTS:

LAM FOUNDATION POSTDOCTORAL FELLOWSHIPS

Deadline: September 1

The LAM Foundation is offering postdoctoral fellowships for the study of the cellular and molecular basis of the abnormal smooth muscle proliferation that occurs in the disease, Lymphangiomyomatosis (LAM.) The LAM Post Doctoral 3 year Fellowship Awards provide a maximum of \$150,000 (\$50,000 per year, renewable for up to two additional years). Pilot Project Awards of up to \$25,000 are also available for the initiation of innovative research projects. Candidates must have at least two years of experience, an MD, PhD, or equivalent degree, and perform the work in a laboratory with established expertise in smooth muscle biology or the genetics of tuberous sclerosis. Examples of competitive proposals include those that focus on the genetic regulation of smooth muscle growth or the development of a smooth muscle cell line that is representative of LAM lesion. Mechanistic, hypothesis driven approaches of all types are welcomed. Formalin-fixed LAM tissues, dispersed LAM lung cells, genetic probes and other reagents are available. The deadline for fall applications is **September 1st** and funding begins January 15th of the following year. You may write to The LAM Foundation at 10105 Beacon Hills Drive, Cincinnati, Ohio, 45241 or email lam@one.net. For your convenience, you will find the terms and application form under [Funding for Scientists](#) on the LAM Foundation Web site.



AMERICAN SKIN ASSOCIATION

Deadline: October 4, 2004

Through its national grants and awards program, the ASA has given more than \$3.5 million in recognition and support of research to promising physician/scientists and leading figures in the field, and to research centers at major institutions throughout the country. Its grants program includes:

- \$50,000 Research Scholar Awards
- \$15,000 Research Grants
- \$15,000 Grants for Health Services/Quality of Life/Outcome Studies
- \$7,000 Medical Student Stipends

- Achievement Awards
- Lifetime Achievement Awards

Their website is <http://www.americanskin.org/frameset.htm>

THE FETAL BASIS OF ADULT DISEASE: ROLE OF THE ENVIRONMENT (PAR-04-104)

National Institute of Environmental Health Sciences

APPLICATION RECEIPT DATE: August 12, 2004

<http://grants.nih.gov/grants/guide/pa-files/PAR-04-104.html>

NIH ANNOUNCEMENTS:

HHS PROVIDES GUIDANCE ON FINANCIAL RELATIONSHIPS AND INTERESTS IN RESEARCH INVOLVING HUMAN SUBJECTS

HHS Secretary Tommy G. Thompson today released new guidance for protecting research subjects from possible harm caused by financial conflicts of interest that may arise in research studies. The guidance, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," applies to all human subjects research conducted or supported by HHS agencies or regulated by the Food and Drug Administration.

"All who take part in research deserve the strongest possible protection," Secretary Thompson said. "Openness and honesty help promote ethical research and can only strengthen the research process."

Institutions, institutional review boards (IRBs), researchers and other responsible parties are encouraged to use this guidance to help ensure that any potential conflicts of interest stemming from financial relationships are identified and eliminated or managed with the subject's best interests in mind. The guidance presents a series of points to consider in determining if and how specific financial interests in research can affect the rights and welfare of human subjects, and if so, what actions can be considered to protect those subjects.

As institutions, IRBs and researchers consider potential financial conflicts of interest, they can refer to the guidance for possible mechanisms to manage such conflicts. These mechanisms include:

- Separating institutional responsibility for research activities from management of the institution's financial interests;
- Establishing conflict of interest committees (COICs) or identifying other bodies or persons and procedures to address financial interests in research;
- Using independent organizations to hold or administer the institution's financial interest;
- Determining whether current methods for managing conflicts of interest are adequate for protecting the rights and welfare of human subjects and whether other actions are needed to minimize risks to subjects;
- Determining the kind, amount, and level of detail of information to be provided to research subjects regarding funding and financial interests; and
- Using special measures to modify the informed consent process when a potential or actual financial conflict exists.

In preparing this guidance, the Department considered public comments on an earlier draft guidance published in March 2003. The guidance is available at

<http://ohrp.osophs.dhhs.gov/humansubjects/finreltn/finalguid.pdf>

STUDY ALLOWS RESEARCHERS TO VISUALIZE FORMATION OF A MEMORY For the first time, researchers have used a technique called optical imaging to visualize changes in nerve connections when flies learn. These changes may be the beginning of a complex chain of events that leads to formation of lasting memories. The study was funded in part by the NIH's National Institute of Neurological Disorders and Stroke (NINDS) and appears in the May 13, 2004, issue of "Neuron".*

Scientists have long been captivated by the questions of how memories form and how they are represented in the brain. The answers to these questions may help researchers understand how to treat or prevent memory problems, drug addiction, and other human ailments. Thousands of changes in gene expression, neuron formation, nerve signaling, and other characteristics may be involved in the formation of just a single memory. Scientists refer to any learning-induced change in the brain as a "memory trace."

In the new study, Ronald L. Davis, Ph.D., and colleagues at Baylor College of Medicine in Houston developed fruit flies with special genes that caused the flies' neuronal connections to become fluorescent during nerve signaling (synaptic transmission). They then exposed the flies to brief puffs of an odor while they received a shock. This caused them to learn a new association between the odor and the shock - a type of learning called classical conditioning.

Using a high-powered microscope to watch the fluorescent signals in flies' brains as they learned, the researchers discovered that a specific set of neurons, called projection neurons, had a greater number of active connections with other neurons after the conditioning experiment. These newly active connections appeared within 3 minutes after the experiment, suggesting that the synapses which became active after the learning took place were already formed but remained "silent" until they were needed to represent the new memory. The new synaptic activity disappeared by 7 minutes after the experiment, but the flies continued to avoid the odor they associated with the shock.

This is the first time that optical imaging has been used to visualize a memory trace, Dr. Davis says. "It's phenomenally powerful, like a movie appearing in front of you," he adds. The study suggests that the earliest representation of a new memory occurs by rapid changes - "like flipping a switch" - in the number of neuronal connections that respond to the odor, rather than by formation of new connections or by an increase in the number of neurons that represent an odor, he adds.

The fact that the flies continued to show a learned response even after the new synaptic activity waned suggests that other memory traces found at higher levels in the brain took over to encode the memory for a longer period of time, Dr. Davis suggests. If so, the rapid changes of nerve transmission that the researchers saw may be the all-important switch that initiates the formation of new memories.

This research suggests a previously unknown mechanism for how memories are formed, Dr. Davis says. While this study looked only at learning related to odors, this newly identified process may be at work in many other kinds of learning as well. It is likely that these or similar mechanisms are important for memory in humans and other animals, he adds.

"This is a remarkable study which uses molecular genetic approaches to visualize memory formation in a living organism. It demonstrates that, in this model system, short term memory involves the recruitment of new synaptic connections into pre-existing ensembles of synapses. It

will be critical to determine whether similar principles control memory formation in higher organisms," says Robert Finkelstein, Ph.D., a program director at NINDS.

The researchers now plan to put fluorescent genes into a variety of other neurons of the brain in order to determine which ones respond to different kinds of stimuli. This will allow them to learn how the changes they identified affect higher-level neurons. They also hope to begin studying similar mechanisms in other animal models, such as mice.

The NINDS is a component of the National Institutes of Health within the Department of Health and Human Services and is the nation's primary supporter of biomedical research on the brain and nervous system.

*Yu D, Ponomarev A, Davis RL. "Altered representation of the spatial code for odors after olfactory classical conditioning: memory trace formation by synaptic recruitment." 'Neuron', May 13, 2004, Vol. 42, No. 3, pp. 437-449.

TSC TISSUE AVAILABILITY:

If you are interested in obtaining tissue for your research, please contact the Brain and Tissue Bank at 1-800-847-1539 or visit their Web site at: <http://som1.umaryland.edu/braintissuebank>

If you have specific needs for TSC tissue for your research, please contact Vicky Whittemore at vwhittemore1@comcast.net

RESOURCES:

Tsc1 MOUSE STRAIN ESTABLISHED AT NCI-FREDERICK MMHCC REPOSITORY The NCI-Frederick MMHCC Repository is pleased to announce that a colony has been established for the Tsc1 mouse strain: **01XH8, B6;129S4-Tsc1<tm1.1Djk>**. This strain will appear on the MMHCC website (<http://mouse.ncifcrf.gov/>) under "Newly Accepted Strains" until the colony has reached distribution level. The following is a brief phenotypic description of the strain:

***"Tsc1(-/+)* heterozygotes develop kidney cystadenomas and liver hemangiomas. Tsc1 null mutants die at mid gestation."**

NEWS:

TS ALLIANCE CEO RESIGNS Mike Coburn has recently resigned as President and CEO of the Tuberous Sclerosis Alliance. Although all members of the Alliance are sorry to lose his strong leadership, both Mike and the TS Alliance Board of Directors feel that Mike's departure provides a positive step forward for both him and the organization. Clearly he leaves the organization substantially stronger and more effective than it was when he joined as head of staff.

The TSA has begun a concentrated search for a new CEO; in the meantime, an interim CEO will be chosen to continue the momentum that Mike, the TS Alliance Staff, the Board, our volunteers, and associated professionals have all worked so hard to generate.

The staff at the TS Alliance wish Mike Coburn all the best in his future endeavors.

CONGRATULATIONS TO RECIPIENTS OF TSCRIP IDEA DEVELOPMENT AWARDS The Tuberous Sclerosis Complex Research Program (TSCRIP) in the Congressionally Directed Medical Research Program announces the following Idea Development Award recipients for FY03:

WILLIAM G KAE LIN, DANA-FARBER CANCER INSTITUTE
Hypoxia- Inducible Factor Regulation by the TSC2 Tumor Suppressor Protein

BERNARDO SABATINI, HARVARD UNIVERSITY, BOSTON
The Role of TSC1 in the Formation and Maintenance of Excitatory Synapses

DAVID STOKOE, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
The Role of GSK3 in Regulating Hamartin Phosphorylation and Activity in Response to Nutrients and Growth Factors

HOWARD HUGHES MEDICAL INSTITUTE SEEKS UP TO 50 NEW SCIENTISTS HHMI is seeking as many as 50 new scientists in the field of biomedical_research through a national competition announced today._The Institute is looking for candidates from the full range of biological and biomedical inquiry who demonstrate exceptional promise early in their careers_as independent researchers. Nearly 200 universities, medical schools, and_research institutes have been invited to nominate their best scientists for_the competition. Between 30 and 50 scientists will be chosen to join the_Institute in 2005._To read the full announcement, please go to:
<http://www.hhmi.org/news/051304.html>

RESEARCHERS FND BRAIN CELLS DIE DIFFERENTLY IN MALES AND FEMALES Researchers at Children's Hospital of Pittsburgh have found that males and females respond differently to brain injury and therefore, boys with brain injuries may require different life-saving treatments than girls. To read more, visit:
<http://www.womenshealthresearch.org/Ojascripts/dropinnav.htm?sbb/news.htm>

SINGLE CANCER GENE HAS PROFOUND EFFECTS Massachusetts Institute of Technology researcher Tyler Jacks, Ph.D. has discovered that a gene commonly mutated in a wide range of cancers can single-handedly trigger pre-cancerous changes in cells. The discovery demonstrates that the oncogene, K-ras, can initiate tumor development in ways that were previously unappreciated. The finding that mutant K-ras alone can cause rapid cell proliferation challenges one of the central tenets of cancer biology -- that the cooperative action of two oncogenes is required to initiate the transformation of cells to a cancerous state. Research published in the April 30, 2004, issue of Cancer Cell. For the full story, go to
<http://www.hhmi.org/news/jacks3.html>

NEW FUNCTIONAL ASSAYS FOR MULTIDRUG RESISTANCE Intrinsic and acquired drug resistance to various classes of chemically diverse chemotherapy agents (referred to as

"MultiDrug Resistance", MDR) represents a major obstacle in modern cancer chemotherapy. The effects of the majority of the most commonly used chemotherapy agents are hindered by MDR mechanisms expressed in cancer cells. With over 1.25 million new cancer cases expected in the US in 2003, over 550,000 patients will succumb to the disease, primarily due to the failure of chemotherapy protocols that involve one or, more often, several anti-tumor agents. Overall, the MDR phenotype is found in 45-50% of cancer cases across the board. That is why MDR research focused on the development of new anti-tumor pharmaceuticals and treatment protocols is currently one of the focal points of attention of the international cancer research and biotechnology communities. Read more at: www.biosciencetechnology.com

PROTEINS ARE OFTEN SPLICED BY A SLICE OF ALTERNATIVE SPLICE

From Genomics & Proteomics magazine May issue) by Vivien Marx, *G&P Senior Editor* Who, except a small number of genomic clochards, would like to dig through genomic garbage? asked Wojciech Makalowski, PhD, from the Institute of Molecular Evolutionary Genetics at Pennsylvania State University, State College, Pa., in an article in the journal Science [W. Makalowski, vol. 300, pp. 1246-1247 (23 May 2003)]. The group of rather proud clochards, which includes Makalowski, is growing as scientists increasingly realize that within the code of the derided 'junk DNA' sequences lies insight into protein complexity as well as an enhanced understanding of certain genetic diseases. The article is on the Web at: www.genpromag.com

CRG LAUNCHES PUBLIC RESOURCE ON GENETICS AND THE LAW The Genetics and the Law Project, an initiative of the Council for Responsible Genetics (CRG), has recently released an expansive, searchable online clearinghouse of information on emerging legal developments in human genetics. Through its new website, <http://www.genelaw.info>, the project offers six original, in-depth reports and a unique database of court cases and legislation in genetics. This resource will provide critical guidance to patients, lawyers, and healthcare stakeholders in making sense of rapid changes in science and the law.

"For anyone confronted by the challenges and opportunities in human genetics, this is an indispensable tool," said Dr. Paul Billings, medical geneticist and Chair of the Council for Responsible Genetics. "The materials it contains will help you keep abreast of how the law is shaping standards of care in genomic medicine and many other areas."

Features of the new website include:

- Detailed summaries of statutes in all fifty states and federal bills affecting genetic privacy and discrimination, many of which provide stricter protections than the federal Health Insurance Portability and Accountability Act.
- Over one hundred court decisions, settlements, pending litigation, and case studies covering a broad range of disputes over the use of genetic technologies and information. Reproductive genetics, medical malpractice, and workplace and insurance discrimination are a few of the topics among the cases documented.
- Informed legal perspectives from leading scholars and experts affiliated with the project, through featured articles and an eighty-page series of original reports.

The Genetics and the Law Project is funded by grants from the California Healthcare Foundation and The Robert Wood Johnson Foundation and supported by excellent guidance from the CRG Working Group on Genetics and the Law. For more information on the project, go to <http://www.genelaw.info> or contact Dr. Sujatha Byravan at 617-868-0870.

NEW TSC PUBLICATIONS:

TSC BASIC SCIENCE HIGHLIGHT: Sen B, Wolf DC, Hester SD (2004) **The transcriptional profile of the kidney in Tsc2 heterozygous mutant Long Evans (Eker) rats compared to wild-type.** *Mutat Res* 549(1-2):213-24

Hereditary renal cell carcinoma (RCC) in Eker rats results from an inherited insertional mutation in the Tsc2 tumor suppressor gene and provides a valuable experimental model to characterize the function of the Tsc2 gene product, tuberlin in vivo. The Tsc2 mutation predisposes the Eker rat to develop renal tumors at an early age. The exact mechanism of Tsc2 mediated tumor suppression is not known, however, there is evidence that it is most likely mediated by changes in cell cycle regulation via the PI3K/Akt pathway. The study by Sen and coworkers was designed to identify if gene expression was different in Tsc2 heterozygous mutant rat kidney compared to wild-type and if any of those differences are associated with tumorigenesis. cDNA microarray analysis of the untreated Tsc2 (+/-) mutant Long Evans (Eker) rat was compared to the Tsc2 (+/+) wild-type Long Evans rat to search for patterns that might be indicative of the intrinsic role of Tsc2. Of 4395 genes queried, 3.2% were significantly altered in kidneys from heterozygous mutant rats, of which 110 (76%) were up-regulated and 34 (24%) were down-regulated relative to the wild-type. The genes with altered expression belonged to the functional categories of cell cycle regulation, cell proliferation, cell adhesion and endocytosis. Many of these genes appear to be directly or indirectly regulated by the PI3K/Akt pathway. In addition to the PI3K/Akt pathway, other signaling pathways were also differentially expressed in Tsc2 mutant Eker rat kidneys compared to wild-type rats. The gene expression profiles of the Tsc2 heterozygous mutant and wild-type animals highlight new pathways for investigation that may be associated with the tumorigenic activity of tuberlin loss and correlate with the enhanced susceptibility of the Tsc2 mutant animal's tendency to develop renal cell carcinoma.

TSC CLINICAL SCIENCE HIGHLIGHT: Lopez-Lopez J, Rodriguez-De-Rivera-Campillo E, Marques-Soares MS, Finestres-Zubeldia F, Chimenos-Kustner E, Rosello-Llabres X (2004) **Tuberous sclerosis and its oral manifestations. A clinical case.** *Med Oral* 9(3):216-23 [Article in English, Spanish]

Tuberous sclerosis (TS) is a congenital anomaly in the development of the embryo which is transmitted through the autosomal dominant gene. It has various forms of clinical expression. It is classified as one of what are known as Phakomatoses (phakos = stain and oma = tumour), which are development anomalies that can result in tumors and/or hamartomas in the nervous system. Lesions in the nervous system are nearly always accompanied by cutaneous anomalies. In this study, Lopez-Lopez and collaborators introduce the case of a woman aged 55, diagnosed several years earlier with Tuberous Sclerosis, who attended for intraoral lesions which were clinically compatible with fibromata. These lesions of fibrous appearance occurred above all on the lower lip and in both cheeks' mucous membranes, little mentioned in the literature as a site for such a manifestation of TS. The pathological anatomy suggested lesions compatible with angiomyolipoma. In addition, the data referring to TS are reviewed; its implications for the mouth are described; and histopathological results are used to examine the significance of the word angiomyolipoma.

TSC PUBLICATIONS:

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from ovarian cancer: a case report] *G Chir* 25(1-2):27-9 [Article in Italian]

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CONFERENCES:

For a complete listing of conferences, visit the TS Alliance website at:
<http://216.33.101.121/Research/upcoming%20conferences.asp>

May 26, 2004

HIPAA and the Privacy Rule: One Year Into Privacy Rule Implementation

Ronald Regan Building and International Trade Center, Washington, DC

To register: <http://www.capconcorp.com/hipaa04/>

June 23-24, 2004

Sixth Annual NIH SBIR/STTR Conference

Natcher Conference Center, NIH, Bethesda, MD

Agenda and registration information are available at the conference website:

<http://grants.nih.gov/grants/funding/sbirconf2004/index.htm>

June 23-25, 2004

Conference about Complexities of Co-Occurring Medical Conditions

Marriott Wardman Park, Washington, DC

More information on the conference and registration is available at:

<http://www.CCCconference.com>

September 16-18, 2004

TSC International Research Conference 2004

TSC Genes - Function and Dysfunction - From Molecular Biology to Therapeutic Advances

Organized by the Tuberous Sclerosis Association of Great Britain

Queens' College, University of Cambridge, Cambridge UK

Deadline for Submission of Poster Abstracts for late breaking research will be accepted until August 1, 2004.

See Tuberous Sclerosis Association Web site for additional information and forms at:

<http://www.tuberous-sclerosis.org/research/conference/index.shtml>

For any queries please contact Ann Hunt at: research@tuberous-sclerosis.org

or telephone/fax: 44 (0)1993 881238

Save the date! May 4-5, 2006

TSC International Research Conference 2006

Berlin, Germany

More information coming soon!

ARCHIVED ISSUES OF TSC ALERT:

December 2002 TSC Alert

<http://www.tsalliance.org/research/tsc%20alert.asp>

January 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alert012203.asp>

February 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alert021003.asp>

March 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alert030403.asp>

April 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alert040103.asp>

May 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alertdefault.asp>

June 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alert060103.asp>

July 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alert72703.asp>

August 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC080103.asp>

September 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alert091503.asp>

October 2003 TSC Alert - Coming soon!

November 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alert112403.asp>

December 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alertdefault.asp>

January 2004 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alert%20default.asp>

February/March 2004 TSC Alert

Coming soon!

April 2004 TSC Alert

Coming soon!