



TSC ALERT

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October/November 2004

Welcome to the October/November 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 December 2004 *TSC Alert* contact: Vicky.Whittemore@tsalliance.org

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IMPORTANT DEADLINES:

TUBEROUS SCLEROSIS ALLIANCE

Deadline for Letters of Intent: November 12, 2004
(See information below in Grant Announcements)

TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM (TSCRCP) IN THE CDRMP

Deadline: February 22, 2005
(See information below in Grant Announcements)

TSC/LAM Research Conference – Call for Abstracts!

Deadline for submission of abstracts: January 14, 2005

Deadline for submission of Late-breaking Abstracts: March 15, 2005

Deadline for Registration: February 18, 2005

(See information below in Conferences)

SOLICITING NOMINATIONS FOR MANUEL R. GOMEZ AWARD

Deadline for submission of nominations: February 1, 2005

(See information below in News)

GRANT ANNOUNCEMENTS:

TUBEROUS SCLEROSIS ALLIANCE

Deadline for Letters of Intent: November 12, 2004

The Tuberous Sclerosis Alliance has released a Request for Applications (RFA). Funding will be provided for postdoctoral fellows, junior and senior investigator awards, as well as for conference grants. A Letter of Intent (LOI) is required prior to submission of a grant application and the PI will be invited to submit a complete grant proposal by the January 28, 2005 deadline. These grants are available to all clinical and basic researchers for proposals pertaining to TSC and are not restricted to grants in the U.S.A.

For more information, see the TS Alliance Web site at: <http://www.tsalliance.org>

TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM (TSCR) IN THE CDMRP

Deadline: February 22, 2005

The Fiscal Year 2005 (FY05) Defense Appropriations Act provides \$3.2 million to the Department of Defense Tuberous Sclerosis Complex Research Program (TSCR) to support innovative research directed toward improved prevention, diagnosis, and treatment of TSC. This program is administered by the US Army Medical Research and Materiel Command through the Office of the Congressionally Directed Medical Research Programs (CDMRP).

FY05 TSCR Program Announcements for the following mechanisms are expected to be released in early **November 2004**, with receipt of electronic submissions due **February 22, 2005 at 5:00 p.m. Eastern time:**

- **Natural History Study Awards - New**
- **Natural History Development Awards**
- **Concept Awards**
- **Idea Development Awards**

Detailed descriptions of each mechanism will be provided in the FY05 TSCR Program Announcements, which are expected to be posted on the CDMRP website in early November. Requests for e-mail notification of the Program Announcement release may be sent to prequest@constellagroup.com. For more information about the TSCR or other CDMRP-

sponsored programs, please visit the CDMRP website at:
<http://cdmrp.army.mil/pubs/press/05tsrpfundopps.htm>

SMALL GRANTS PROGRAM FOR CANCER EPIDEMIOLOGY (PAR-04-159)

National Cancer Institute

Application Receipt Date(s): November 21, 2005; March 20, 2006;
July 20, 2006; November 20, 2006; March 20, 2007; July 20, 2007;
November 20, 2007; March 20, 2008; July 21, 2008; November 21, 2008
<http://grants.nih.gov/grants/guide/pa-files/PAR-04-159.html>

**NIH ANNOUNCES REVISED POLICY: APPLICATIONS THAT INCLUDE CONSORTIUM/
CONTRACTUAL FACILITIES AND ADMINISTRATIVE COSTS (NOT-OD-05-004)**

National Institutes of Health

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-004.html>

SKIN DISEASES RESEARCH CORE CENTERS (RFA-AR-05-002)

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Application Receipt Date(s): May 24, 2005

<http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-05-002.html>

TYPICAL/DISORDERED LANGUAGE: PHENOTYPE ASSESSMENT TOOLS (RFA-DC-05-001)

National Institute on Deafness and Other Communication Disorders

National Institute of Child Health and Human Development

Application Receipt Date(s): February 24, 2005

<http://grants.nih.gov/grants/guide/rfa-files/RFA-DC-05-001.html>

REVIEW OF RANKING DATA (NOT-OD-05-008)

National Institutes of Health

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-008.html>

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 or Vicky.whittemore@tsalliance.org

NEW TSC PUBLICATIONS:

TSC BASIC SCIENCE HIGHLIGHT: Dong J, Pan D (2004) Tsc2 is not a critical target of Akt during normal Drosophila development. Genes Dev 2004 Oct 1 [Epub ahead of print]

Signaling by insulin and target of rapamycin are both required for cell growth, but their interrelationships remain poorly defined. It was reported that Akt, an essential component of the insulin pathway, stimulates growth by phosphorylating and inhibiting tuberous sclerosis complex 2 (TSC2). Here Dong and Pan evaluated this model genetically in Drosophila by engineering Tsc2 mutants in which the Akt phosphorylation sites were changed to nonphosphorylatable or phospho-mimicking residues. Strikingly, such mutants completely rescued the lethality and cell growth defects of Tsc2-null mutants. Taken together, their data suggest that Tsc2 is not a critical substrate of Akt in normal Drosophila development.

Note: Dr. Duoqia D.J. Pan has recently accepted a position as Associate Professor in the Department of Molecular Biology and Genetics at Johns Hopkins University.

TSC CLINICAL SCIENCE HIGHLIGHT: Goh S, Butler W, Thiele EA (2004) Subependymal giant cell tumors in tuberous sclerosis complex. Neurology 63(8):1457-61

This study set out to describe the clinical presentations, radiologic features, and postoperative outcomes of a clinic-based population of patients with subependymal giant cell tumors (SGCT) and tuberous sclerosis complex (TSC) and to redefine and reclassify SGCT based on radiologic, clinical, and pathologic criteria. Of 134 TSC patients evaluated from December 2001 to November 2003, 11 (8.2%) had undergone resection of a pathologically confirmed SGCT. The authors reviewed the medical records of each case. Follow-up ranged from 2 months to 36 years. Four individuals were asymptomatic at the time of resection while the other seven presented subacutely with fatigue, decreased appetite, headache, increased seizure frequency, visual field deficit, cognitive decline, or behavioral problems. Poor outcomes occurred in all patients aged 11 years or older at the time of resection. Subependymal giant cell tumors in patients with TSC appear to be of mixed glioneuronal lineage, and, therefore, the current practice of classifying these tumors as astrocytomas merits revision. The clinical diagnosis of SGCT should be made for subependymal lesions in TSC that are associated with symptoms, papilledema, or radiologic evidence of hydrocephalus or interval growth. A diagnosis of probable SGCT should be made when a lesion has the potential to cause obstruction based on size or location. Annual screening by MRI with or without contrast is indicated until at least 21 years of age even if subependymal nodules are absent on initial imaging. A diagnosis of SGCT or probable SGCT warrants more frequent monitoring or surgical intervention.

TSC PUBLICATIONS:

Alvarez Rodriguez E, Torres Garate R, Rojano Martin B, Gutierrez Larrainzar A, Maroto Rubio M, Lozano Tonkin C (2004) Renal angiomyolipoma and tuberous sclerosis complex.] An Med Interna 21(9):469 [Article in Spanish]

Aron M, Goel R, Kesarwani PK, Seth A, Gupta NP (2004) Upper pole access for complex lower pole renal calculi. BJU Int 94(6):849-52

Bailey SN, Sabatini DM, Stockwell BR (2004) Microarrays of small molecules embedded in biodegradable polymers for use in mammalian cell-based screens. *Proc Natl Acad Sci U S A* 2004 Nov 8 [Epub ahead of print]

Bhende P, Babu K, Kumari P, Krishnakumar S, Biswas J (2004) Solitary retinal astrocytoma in an infant. *J Pediatr Ophthalmol Strabismus* 41(5):305-7

Chatelain D, Sevestre H, Zaher H, Flamant M, Brazier F, Geslin G, Dupas JL, Regimbeau JM (2004) Unusual complication of tuberous sclerosis complex. *Gut* 53(11):1552

Dong J, Pan D (2004) Tsc2 is not a critical target of Akt during normal *Drosophila* development. *Genes Dev* 2004 Oct 1 [Epub ahead of print]

Fadare O, Parkash V, Yilmaz Y, Mariappan MR, Ma L, Hileeto D, Qumsiyeh MB, Hui P (2004) Perivascular epithelioid cell tumor (PEComa) of the uterine cervix associated with intraabdominal "PEComatosis": A clinicopathological study with comparative genomic hybridization analysis. *World J Surg Oncol* 2004 Oct 19 2(1):35 [Epub ahead of print]

Farfal S, Marchelek M, Dutkiewicz G, Rozanski J, Ciechanowski K, Maleszka R (2004) [Tuberous sclerosis--symptoms, diagnosis and treatment] *Pol Merkuriusz Lek* 16(96):589-91 [Article in Polish]

Goh S, Butler W, Thiele EA (2004) Subependymal giant cell tumors in tuberous sclerosis complex. *Neurology* 63(8):1457-61

Granata A, Sessa A (2004) Quiz page. Tuberous sclerosis complex. *Am J Kidney Dis* 44(5):A39, e79-80

Hardie DG (2004) The AMP-activated protein kinase pathway - new players upstream and downstream. *J Cell Sci* 117(Pt 23):5479-87

Hes O, Michal M (2004) Renal oncocytic angiomyolipoma. *Int J Surg Pathol* 12(4):421

Jansen FE, Notenboom RG, Nellist M, Goedbloed MA, Halley DJ, de Graan PN, van Nieuwenhuizen O (2004) Differential localization of hamartin and tuberin and increased S6 phosphorylation in a tuber. *Neurology* 63(7):1293-5

Kun Rebecca Tang Chark-Man Tai Tai-Keung Ng KY (1999) Tuberous sclerosis in a Chinese baby presented with a pleural effusion and cardiac tumour during prenatal period. *J Obstet Gynaecol* 19(4):429-30

Lee C, Kim JS, Waldman T (2004) PTEN gene targeting reveals a radiation-induced size checkpoint in human cancer cells. *Cancer Res* 64(19):6906-14

Manning BD (2004) Balancing Akt with S6K: implications for both metabolic diseases and tumorigenesis. *J Cell Biol* 167(3):399-403

Mashhood AA, Amjad M (2004) Unilateral tuberous sclerosis complex. *J Coll Physicians Surg Pak* 14(10):628-30

Mboyo A, Flurin V, Foulet-Roge A, Bah G, Orain I, Weil D (2004) Conservative treatment of a mesenteric lymphangiomyomatosis in an 11-year-old girl with a long follow-up period. *J Pediatr*

Surg 39(10):1586-9

Miyama S, Goto T (2004) Leptomeningeal angiomatosis with infantile spasms. *Pediatr Neurol*. 2004 Nov;31(5):353-356.

Miyata H, Chiang AC, Vinters HV (2004) Insulin signaling pathways in cortical dysplasia and TSC-tubers: Tissue microarray analysis. *Ann Neurol* 2004 Sep 28 56(4):510-519 [Epub ahead of print]

Nellist M, Sancak O, Goedbloed MA, Rohe C, van Netten D, Mayer K, Tucker-Williams A, van den Ouweland AM, Halley DJ (2004) Distinct effects of single amino-acid changes to tuberin on the function of the tuberin-hamartin complex. *Eur J Hum Genet*. 2004 Oct 13 [Epub ahead of print]

O'Callaghan FJ, Noakes MJ, Martyn CN, Osborne JP (2004) An epidemiological study of renal pathology in tuberous sclerosis complex. *BJU Int* 94(6):853-7

Schuster TG, Ferguson MR, Baker DE, Schaldenbrand JD, Solomon MH (2004) Papillary Renal Cell Carcinoma Containing Fat Without Calcification Mimicking Angiomyolipoma on CT. *AJR Am J Roentgenol* 183(5):1402-4

Schwarzbraun T, Vincent JB, Schumacher A, Geschwind DH, Oliveira J, Windpassinger C, Ofner L, Ledinegg MK, Kroisel PM, Wagner K, Petek E (2004) Cloning, genomic structure, and expression profiles of TULIP1 (GARNL1), a brain-expressed candidate gene for 14q13-linked neurological phenotypes, and its murine homologue. *Genomics* 84(3):577-86

Shuhaiber H, Bolton S, Alfonso I, Dunoyer C, Yaylali I (2004) Cerebral regional oxygen fluctuations and decline during clinically silent focal electroencephalographic seizures in a neonate. *J Child Neurol* 19(7):539-40

Stipic Markovic A, Pekic P, Pevec B, Rudan D, Ostojic S, Dzebro S (2004) [Lymphangioliomyomatosis.] *Acta Med Croatica* 58(3):233-6 [Article in Croatian]

Takei N, Inamura N, Kawamura M, Namba H, Hara K, Yonezawa K, Nawa H (2004) Brain-derived neurotrophic factor induces mammalian target of rapamycin-dependent local activation of translation machinery and protein synthesis in neuronal dendrites. *J Neurosci* 24(44):9760-9

Wei J, Chiriboga L, Mizuguchi M, Yee H, Mittal K (2004) Expression profile of tuberin and some potential tumorigenic factors in 60 patients with uterine leiomyomata. *Mod Pathol* 2004 Oct 01 [Epub ahead of print]

Weisman R, Roitburg I, Nahari T, Kupiec M (2004) Regulation of leucine uptake by tor1+in *Schizosaccharomyces pombe* is sensitive to rapamycin. *Genetics* 2004 Sep 30 [Epub ahead of print]

Zhang SH, Cong WM, Xian ZH, Wu WQ, Dong H, Wu MC (2004) [Morphologic variants and immunohistochemical features of hepatic angiomyolipoma.] *Zhonghua Bing Li Xue Za Zhi* 33(5):437-40 [Article in Chinese]

Zhe X, Yang Y, Schuger L (2004) Imbalanced Plasminogen System in Lymphangioliomyomatosis: Potential Role of Serum Response Factor. *Am J Respir Cell Mol Biol* 2004 Oct 28 [Epub ahead of print]

CONFERENCES:

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

December 3-7, 2004

American Epilepsy Society Meeting

Convention Center, New Orleans, LA

- ***Stop by the TS Alliance exhibit at the meeting!***

January 27-28, 2005

National Coalition for Health Professional Education in Genetics (NCHPEG) & Genetics Resources on the Web (GROW) 8th Annual Meeting: Focus on Family History

Hyatt Regency Bethesda, Bethesda, MD

For more information: <http://www.nchpeg.org>

February 19-20, 2005

West Coast Regional TSC Conference

Mission Inn, Riverside, CA

Sponsored and organized by the Community Alliance of the Tuberous Sclerosis Alliance

For more information, contact April Cooper at ACoope@ardenrealty.com

April 8-10, 2005

TSC/LAM Research Conference & TSC Adult Conference

The Hyatt Regency, Downtown Cincinnati, OH

Organized by the Tuberous Sclerosis Alliance, LAM Foundation, and Rare Lung Disease Consortium

The Tuberous Sclerosis Alliance and the LAM Foundation invite you to attend the first joint TSC/LAM conference in Cincinnati, Ohio in April 2005. Sessions will include:

- The TSC Genes in the Brain – What Do They Do?
- Signaling Pathways and Basic Biology of TSC1/TSC2
- TSC-LAM Translational Research
- What Causes Epilepsy in TSC?
- Behavioral Phenotypes in TSC
- Late-Breaking Science and Roadmap for a Cure for TSC

CALL FOR ABSTRACTS

Platform and poster presentations will be selected from submitted abstracts based on scientific merit and thematic considerations. The application and instructions are enclosed and may also be completed electronically or downloaded from the Tuberous Sclerosis Alliance Web site at

<http://www.tsalliance.org> or The LAM Foundation website at <http://lam.uc.edu>

Deadline for submission of abstracts: January 14, 2005

Deadline for submission of Late-Breaking TSC Abstracts: March 15, 2005

Deadline for Registration: February 18, 2005

For more information, Call for Abstracts, Agenda and Registration information:

<http://www.tsalliance.org>

Save the date! May 4-5, 2006
TSC International Research Conference 2006
Berlin, Germany
More information coming soon!

NEWS:

SOLICITING NOMINATIONS FOR MANUEL R. GOMEZ AWARD The Tuberous Sclerosis Alliance is soliciting nominations for the Manuel R. Gomez Award. Individuals who have made significant contributions toward our understanding of tuberous sclerosis complex (TSC) either through their research and/or by providing clinical care for individuals with TSC may be nominated. The award will be presented at the TSC/LAM Research Conference in Cincinnati, Ohio in April 2005.

Nominations should include a letter of nomination detailing the individual's contribution(s) to TSC research and/or clinical care and a complete and up-to-date copy of their CV. Nominations should be submitted to:

Manuel R. Gomez Award Committee
Tuberous Sclerosis Alliance
801 Roeder Road, Suite 750
Silver Spring, MD 20910

Deadline for submission of nominations is February 1, 2005.

TEXTPRESSO'S RICHER BLEND OF SCIENTIFIC DATA Frustrated that the volume and increasing complexity of the scientific literature might make it impossible for researchers to keep pace, HHMI researchers have developed Textpresso, a new text-mining system that sifts through the literature and identifies relevant information nearly as well as human document curators. This research Paul W. Sternberg, Ph.D., at the California Institute of Technology was published in the October 04, 2004, issue of Public Library of Science (PLoS) Biology. For the full story, go to <http://www.hhmi.org/news/sternberg2.html>

HUMAN BLOOD GENOMICS: DISTINCT PROFILES FOR GENDER, AGE AND NEUROFIBROMATOSIS TYPE Dr. Yang Tang and coworkers demonstrated that the NF1 gene mutation or the presence of the Y chromosome can cause specific gene expression patterns in peripheral blood cells even though no obvious phenotypes are observed in the blood. This finding suggests that peripheral blood can be used to study functional genomics and phenotypes of genetic diseases and blood genomic expression profiling holds promise for providing molecular markers for the effects of genetic diseases on end-organs. For more information: http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T07-4BC2MB8-1&_coverDate=01%2F01%2F2004&_alid=211890890&_rdoc=1&_fmt=&_orig=search&_qd=1&_cdi=4855&_sort=d&_view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=5b8b5b0e69a30a01ae2818d764974084

HHMI UNVEILS SCIENTIFIC PROGRAM AND RECRUITMENT STRATEGY FOR THE JANELIA FARM RESEARCH CAMPUS Howard Hughes Medical Institute (HHMI) announced

today that it is commencing recruitment for scientific group leaders for its Janelia Farm Research Campus, which is currently being constructed in Ashburn, Virginia. The Institute has also identified two broad areas of scientific inquiry that are well suited to Janelia Farm: The identification of general principles that govern how information is processed by neuronal circuits; and the development of imaging technologies and computational methods for image analysis. As HHMI's first freestanding campus, Janelia Farm will provide a setting in which small research groups can explore fundamental biomedical questions in a highly collaborative, interdisciplinary culture. The \$500 million campus will open in late 2006. To read the full story, go to <http://www.hhmi.org/news/100404.html>

WITHOUT DOPAMINE, NEURONS CONTINUE TO FIRE NORMALLY Researchers are learning whether normal neuron behavior depends on the ability to produce an essential neurotransmitter. Recent studies in living mice by Richard D. Palmiter, Ph.D., at the University of Washington School of Medicine, indicate that dopamine-producing neurons are capable of triggering nerve impulses even when they are deprived of dopamine. This research was published in the September 07, 2004, issue of Proceedings of the National Academy of Sciences. For the full story, go to <http://www.hhmi.org/news/palmiter2.html>

NIH Releases Guidelines on DNA Use

The NIH has released a notice, "Compliance with The NIH Guidelines for Research Involving Recombinant DNA Molecules" reminding researchers of rules and highlights some of the required compliance activities.

RESEARCHERS BOWLED OVER BY GLUTAMATE TRANSPORTER'S ELEGANT

ARCHITECTURE X-ray crystallography studies BY Eric Gouaux, Ph.D. at Columbia University College of Physicians and Surgeons, reveal the inner beauty of a transporter protein that vacuums up the neurotransmitter glutamate. To solve the structure, HHMI scientists turned to an extreme organism, *Pyrococcus horikoshii*, a bacterium that has adapted to life in boiling undersea vents. The studies of the glutamate transporter's structure could aid the development of new drugs to treat a wide range of disorders. For the full story, go to <http://www.hhmi.org/news/gouaux.html>

NEW ANIMAL LAW WEB SITE

The National Association for Biomedical Research has announced the launch of a new animal law Web site for anyone looking for information on animals and the law.

Public Comment Period on Public Access to Research

NIH has released a notice on "Enhanced Public Access to NIH Research Information," This notice is to announce and to seek public comments regarding NIH's plans to facilitate enhanced public access to NIH health related research information.

Public Workshop on Stem Cell Research Guidelines

The National Research Council is organizing a public workshop, "Guidelines for Human Embryonic Stem Cell Research" October 12-13, 2004, in Washington, DC, at the National Academy of

Sciences. The workshop will explore scientific and ethical aspects of issues related to human embryonic stem cell research, including nuclear transplantation (the use of somatic cell nuclear transfer to create stem cells) among other topics, and provide a forum for the expression of different viewpoints about the appropriate scope and content of guidelines for this emerging research field.

NIMH GRANT TO EXPLORE GENETICS OF AUTISM The National Institute of Mental Health (NIMH), part of the National Institutes of Health, announced this week a 3-year, \$3 million grant to Johns Hopkins University to study the genetic factors underlying autism.

In an average year, 2 to 6 new cases of Autism, a neuropsychiatric disorder, arise per 1,000 children. While at least 80 percent of the disorder is due to hereditary factors, experts believe it develops from an interaction between environmental factors and multiple unknown genes. The Johns Hopkins research team, led by Aravinda Chakravarti, Ph.D., proposes to use new genetic analysis technologies to dissect the complex neuropsychiatric traits of autism.

"Although the role of hereditary factors in autism is not in doubt, their nature remains elusive and no single causal gene has yet been identified," said NIMH Director Thomas R. Insel, M.D. "This initiative is part of a group of projects put forward by NIMH to begin unraveling the underlying genetics of autism."

The study will apply novel statistical methods and molecular technologies to identify specific genetic markers, or polymorphisms -- naturally-occurring genetic variations -- that may be related to autism. To accomplish this, the researchers will use DNA and clinical data from the NIMH Human Genetics Initiative (<http://www.nimhgenetics.org>) and the Autism Genetic Research Exchange (<http://www.agre.org>), two large repositories of research resources available to the scientific community. The investigators aim to identify specific gene variants that contribute to vulnerability to autism.

ARCHIVED ISSUES OF TSC ALERT:

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