



TSC ALERT

Edited by Vicky Holets Whittemore, Ph.D. & Cheryl Dunigan, Ph.D.
May 9, 2003

Welcome to the May edition of *TSC Alert* – an online research newsletter for individuals interested in tuberous sclerosis complex (tsc) research. This online newsletter contains information of interest to the tsc research community. Please forward this newsletter to colleagues who are interested in tsc research.

To be added to the mailing list for *TSC Alert* and/or to submit information for the June 2003 *TSC Alert* contact: Vicky.Whittemore@tsalliance.org

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GRANT ANNOUNCEMENTS:

Tuberous Sclerosis Complex Research Program (TSCRCP) in the Congressionally Directed Medical Research Program, Department of Defense

Deadline for submission of applications: August 20, 2003

Idea Development Awards in the TSCRCP are designed to encourage innovative research directed towards a better understanding of the roles and functions of the proteins produced by the *TSC1* and *TSC2* tumor suppressor genes. They are intended to stimulate and reward innovative research ideas that may be viewed as high risk but have the potential for high gain in scientific and clinical knowledge. Specific interests of the TSCRCP for FY03 include proposals that:

- Address the signaling pathways involving *TSC1* and *TSC2*; or

- Examine the way(s) in which the loss of *TSC1* or *TSC2* contribute(s) to disease phenotypes.

[TSRP Funding Opportunities](#) | [Synopsis of TSRP Award Mechanisms](#) | [TSRP Press Release](#)

The LAM Foundation

The LAM Foundation is offering post doctoral fellowships for the study of the cellular and molecular basis of the abnormal smooth muscle proliferation that occurs in the disease Lymphangioliomyomatosis (LAM). Application deadline is September 1st and funding begins January 15th of the following year. For additional information, contact:

The LAM Foundation
 Sue Byrnes, Director
 10105 Beacon Hills Drive, Cincinnati, OH 45241
 Telephone: 513-777-6889
 FAX: 513-777-4109
 E-mail: lam@one.net
 Web site: <http://lam.uc.edu>

The Epilepsy Foundation

The Epilepsy Foundation supports a series of grants to advance understanding of epilepsy that will lead to better treatment, more effective prevention, and ultimately to a cure. Their grants fund a wide range of researchers including students, junior level and senior level investigators. For researchers intending to apply for a grant, please read their [guidelines for funding](#) research proposals.

The **Shire Targeted Investigations: Quality of Life** research grant is to stimulate research related to interventions that may improve some aspect of the quality of life for children with epilepsy. Applications should place an emphasis on outcome-oriented psychosocial research.
Deadline: August 15, 2003.

Other grant opportunities have deadlines in Fall 2003. For additional information contact:

The Epilepsy Foundation
 4351 Garden City Drive
 Landover, MD 20785-7223
 Telephone: (800) 332-1000
 Web site: <http://www.epilepsyfoundation.org/research/grants.html>

NIH ANNOUNCEMENTS:

- **Dr. Katz's** statement to the appropriations subcommittee is available at: http://www.niams.nih.gov/ne/reports/congree_rep/cj2004/open2004.htm
- The **President's Council on Bioethics** is soliciting public comments on a broad range of topics including issues related to assisted reproduction, embryo research, and human genetics. The deadline for comments is April 15.
<http://frwebgate4.access.gpo.gov/cgi-bin/waisgate.cgi?WAIISdocID=00103715000+0+0+0&WAIISaction=retrieve>
- **The HIPAA Privacy Rule and Research** - The Department of Health and Human Services (HHS) issued the Standards for Privacy of Individually Identifiable Health

Information (the Privacy Rule) under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) to provide the first comprehensive federal protection for the privacy of personal health information. Many of those who must comply with the Privacy Rule must do so by April 14, 2003. While certain provisions of the Rule specifically concern research and may affect research activities, the Privacy Rule recognizes that the research community has legitimate needs to use, access, and disclose Protected Health Information (PHI) to carry out a wide range of health research protocols and projects. The Privacy Rule protects the privacy of such information while providing ways in which researchers can access and use PHI when necessary to conduct research. For more information, see: <http://privacyruleandresearch.nih.gov>

- **NIH Public Bulletin:** Are you curious about the latest health information and research initiatives at the NIH? Learn about these events and resources and more in this message from the National Institutes of Health (NIH). You can find out where you can visit a Drunken Brain Exhibit, learn about a course on Complementary and Alternative Medicine for the public or find out how to get an interactive Eye Exhibit to your local community mall. View the latest issue of the NIH Public Bulletin: <http://forthepublic.nih.gov/newsbulletins/may2003/>
- The May 2003 issue of the **FYI from the NHLBI** is available online at <http://www.nhlbi.nih.gov/public/may03/index.htm>
- **GENE DISCOVERY FOR COMPLEX NEUROLOGICAL AND NEUROBEHAVIORAL DISORDERS**
(PAS-03-092)
<http://grants.nih.gov/grants/guide/pa-files/PAS-03-092.html>
Contact: Dr. Robert Finkelstein at finkelsr@ninds.nih.gov
- **RFI - NINDS Pilot Clinical Trials Network** [[Brief Description](#)] [[Full Description](#)]
Release Date: 05/01/2003 Announcement Number: NOT-NS-03-008
Program Contact: [Ida Lirette](#) Program Area: [Contracts Management Branch](#), [Clinical Trials](#)
- **Presolicitation Notice - Quality of Life Outcomes in Neurological Disorders** [[Brief Description](#)] [[Full Description](#)]
Release Date: 04/29/2003 Announcement Number: NOT-NS-03-015
Program Contact: [Laurie Leonard](#) Program Area: [Contracts Management Branch](#), [Clinical Trials](#)
Also See: <http://www.eps.gov/spg/HHS/NIH/NINDS/NIH-NINDS-03-04/SynopsisP.html>

NEW TSC PUBLICATIONS:

[New search terms added: Eker, mTOR, dTOR, cortical dysplasia]

Alvarez B, Garrido E, Garcia-Sanz JA, Carrera AC (2003) Phosphoinositide 3-kinase activation regulates cell division time by coordinated control of cell mass and cell cycle progression rate. *J Biol Chem* 2003 Apr 21; [epub ahead of print] <http://www.jbc.org/cgi/reprint/M300663200v1>

Apak A, Haliloglu G, Kose G, Yilmaz E, Anlar B, Aysun S (2003) Mutation analysis of TSC2 gene in 33 Turkish familial cases with tuberous sclerosis. *Turk J Pediatr* 45(1):1-5

Aronica E, Gorter JA, Jansen GH, van Veelen CW, van Rijen PC, Leenstra S, Ramkema M, Scheffer GL, Scheper RJ, Troost D (2003) Expression and cellular distribution of multidrug transporter proteins in two major causes of medically intractable epilepsy: focal cortical dysplasia and glioneuronal tumors. *Neuroscience* 118(2):417-29

Asaki C, Usuda N, Nakazawa A, Kametani K, Suzuki T (2003) Localization of translational components at the ultramicroscopic level at postsynaptic sites of the rat brain. *Brain Res* 972(1-2):168-76

Attyaoui F, Binous MY, Sallami S, Chtourou M, Kbaier I, Horchani A (2003) [Renal angiomyolipomas.] *Tunis Med* 81(1):1-4 [Article in French]

Badawi RA, Geddes DM (2003) Exertional haemoptysis: LAM and TSC. *Thorax* 58(5):460

Basu S (2003) Akt Inhibits DNA damage by Suppressing p73, p53, Forkhead or all Three? *Cell Cycle* 2(2):69-70

Cepeda C, Hurst RS, Flores-Hernandez J, Hernandez-Echeagaray E, Klapstein GJ, Boylan MK, Calvert CR, Jocoy EL, Nguyen OK, Andre VM, Vinters HV, Ariano MA, Levine MS, Mathern GW (2003) Morphological and electrophysiological characterization of abnormal cell types in pediatric cortical dysplasia. *J Neurosci Res* 72(4):472-86

Cesen-Cummings K, Houston KD, Copland JA, Moorman VJ, Walker CL, Davis BJ (2003) Uterine leiomyomas express myometrial contractile-associated proteins involved in pregnancy-related hormone signaling. *J Soc Gynecol Investig* 10(1):11-20

Chen JS, Kuo LJ, Lin PY, Changchien CR (2003) Angiomyolipoma of the colon: report of a case and review of the literature. *Dis Colon Rectum* 46(4):547-9

Cuccia V, Zuccaro G, Sosa F, Monges J, Lubienieky F, Taratuto AL (2003) Subependymal giant cell astrocytoma in children with tuberous sclerosis. *Childs Nerv Syst* 19(4):232-43

Di Michele F, Verdecchia M, Dorofeeva M, Costamagna L, Bernardi G, Curatolo P, Romeo E (2003) GABA(A) receptor active steroids are altered in epilepsy patients with tuberous sclerosis. *J Neurol Neurosurg Psychiatry* 74(5):667-670

Diehl B, LaPresto E, Najm I, Raja S, Rona S, Babb T, Ying Z, Bingaman W, Luders HO, Ruggieri P (2003) Neocortical Temporal FDG-PET Hypometabolism Correlates with Temporal Lobe Atrophy in Hippocampal Sclerosis Associated with Microscopic Cortical Dysplasia. *Epilepsia* 44(4):559-64

El-Hashemite N, Zhang H, Henske EP, Kwiatkowski DJ (2003) Mutation in TSC2 and activation of mammalian target of rapamycin signalling pathway in renal angiomyolipoma. *Lancet* 361(9366):1348-9

Finlay GA, Hunter DS, Walker CL, Paulson KE, Fanburg BL (2003) The regulation of PDGF production and ERK activation by estrogen is associated with TSC2 gene expression. *Am J Physiol Cell Physiol* [epub ahead of print]

Gao X, Zhang Y, Arrazola P, Hino O, Kobayashi T, Yeung RS, Ru B, Pan D (2002) Tsc tumour suppressor proteins antagonize amino-acid-TOR signalling. *Nat Cell Biol* 4(9):699-704

Glassman D (2003) Laparoscopic donor nephrectomy in a patient with previous upper pole partial nephrectomy. *Urology* 61(1):224

Habib SL, Phan MN, Patel SK, Li D, Monks TJ, Lau SS (2003) Reduced constitutive 8-oxoguanine-DNA glycosylase expression and impaired induction following oxidative DNA damage in the tuberin deficient Eker rat. *Carcinogenesis* 24(3):573-82

Hagemann G, Kluska MM, Redecker C, Luhmann HJ, Witte OW (2003) Distribution of glutamate receptor subunits in experimentally induced cortical malformations. *Neuroscience* 117(4):991-1002

Hennig KM, Neufeld TP (2002) Inhibition of cellular growth and proliferation by dTOR overexpression in *Drosophila*. *Genesis* 34(1-2):107-10

Hino O, Kobayashi T, Momose S, Kikuchi Y, Adachi H, Okimoto K (2003) Renal carcinogenesis: genotype, phenotype and dramatype. *Cancer Sci* 94(2):142-7

Hooth MJ, McDorman KS, Hester SD, George MH, Brooks LR, Swank AE, Wolf DC (2002) The carcinogenic response of Tsc2 mutant Long-Evans (Eker) rats to a mixture of drinking water disinfection by-products was less than additive. *Toxicol Sci* 69(2):322-31

Homolka J, Svobodova L, Slovakova A, Votava V, Polak J (2003) [Lymphangiomyomatosis] *Cas Lek Cesk* 142(2):117-9 [Article in Czech]

Hu MC, Piscione TD, Rosenblum ND (2003) Elevated SMAD1/beta-catenin molecular complexes and renal medullary cystic dysplasia in ALK3 transgenic mice. *Development* 130(12):2753-2766

Hunter DS, Klotzbucher M, Kugoh H, Cai SL, Mullen JP, Manfioletti G, Fuhrman U, Walker CL (2002) Aberrant expression of HMGA2 in uterine leiomyoma associated with loss of TSC2 tumor suppressor gene function. *Cancer Res* 62(13):3766-72

Kim do H, Sarbassov dos D, Ali SM, Latek RR, Guntur KV, Erdjument-Bromage H, Tempst P, Sabatini DM (2003) GbetaL, a Positive Regulator of the Rapamycin-Sensitive Pathway Required for the Nutrient-Sensitive Interaction between Raptor and mTOR. *Mol Cell* 11(4):895-904

Kim NR, Chung MP, Park CK, Lee KS, Han J (2003) Pulmonary lymphangioliomyomatosis and multiple hepatic angiomyolipomas in a man. *Pathol Int* 53(4):231-5

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Kubota H, Obata T, Ota K, Sasaki T, Ito T (2003) Rapamycin-induced translational derepression of GCN4 mRNA involves a novel mechanism for activation of the eIF2alpha kinase GCN2. *J Biol Chem* [epub ahead of print]

Lamblin A, Mulliez E, Lemaitre L, Pattou F, Proye C (2003) [Acute peritonitis: a rare presentation of chylous ascites]. *Ann Chir* 128(1):49-52 [Article in French]

Lee A, Maldonado M, Baybis M, Walsh CA, Scheithauer B, Yeung R, Parent J, Weiner HL, Crino PB (2003) Markers of cellular proliferation are expressed in cortical tubers. *Ann Neurol* 53(5):668-73

Lee DI, McGinnis DE, Feld R, Strup SE (2003) Retroperitoneal laparoscopic cryoablation of small renal tumors: intermediate results. *Urology* 61(1):83-8

Lendvay TS, Marshall FF (2003) The tuberous sclerosis complex and its highly variable manifestations. *J Urol* 169(5):1635-42

Li Y, Inoki K, Vacrasis P, Guan KL (2003) The p38 and MK2 kinase cascade phosphorylates tuberin, the tuberous sclerosis 2 (TSC2) gene product, and enhances its interaction with 14-3-3. *J Biol Chem* 278(16):13663-71

Ligon KL, Echelard Y, Assimacopoulos S, Danielian PS, Kaing S, Grove EA, McMahon AP, Rowitch DH (2003) Loss of *Emx2* function leads to ectopic expression of *Wnt1* in the developing telencephalon and cortical dysplasia. *Development* 130(10):2275-2287

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Mangoni ML, Di Santo S, Esposito S, Codella U, Cappabianca S, Grassi R (2003) [Renal angiomyolipoma as a sign of pulmonary lymphangiomyomatosis (LAM). Case report and review of literature] *Radiol Med (Torino)* 105(1-2):122-6 [Article in Italian]

Matsui T, Nagoshi T, Rosenzweig A (2003) Akt and PI 3-Kinase Signaling in Cardiomyocyte Hypertrophy and Survival. *Cell Cycle* 2(3):220-3

McDorman KS, Chandra S, Hooth MJ, Hester SD, Schoonhoven R, Wolf DC (2003) Induction of transitional cell hyperplasia in the urinary bladder and aberrant crypt foci in the colon of rats treated with individual and a mixture of drinking water disinfection by-products. *Toxicol Pathol* 31(2):235-42

McDorman KS, Hooth MJ, Starr TB, Wolf DC (2003) Analysis of preneoplastic and neoplastic renal lesions in *Tsc2* mutant Long-Evans (Eker) rats following exposure to a mixture of drinking water disinfection by-products. *Toxicology* 187(1):1-12

McDorman KS, Wolf DC (2002) Use of the spontaneous *Tsc2* knockout (Eker) rat model of hereditary renal cell carcinoma for the study of renal carcinogens. *Toxicol Pathol* 30(6):675-80

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Morton LD, Youssef AF, Lloyd E, Kiorpes AL, Goldsworthy TL, Fort FL (2002) Evaluation of carcinogenic responses in the Eker rat following short-term exposure to selected nephrotoxins and carcinogens. *Toxicol Pathol* 30(5):559-64

Nakai M, Nakamura N (2003) [Case report of spontaneous rupture of renal cell carcinoma difficult to be distinguished from angiomyolipoma] *Hinyokika Kyo* 49(2):99-101 [Article in Japanese]

Nojima H, Tokunaga C, Eguchi S, Oshiro N, Hidayat S, Yoshino KI, Hara K, Tanaka N, Avruch J, Yonezawa K (2003) The mTOR partner, Raptor binds the mTOR substrates, p70 S6 kinase and 4E-BP1 through their TOS (TOR signaling) motif. *J Biol Chem* [epub ahead of print]

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- Pan LH, Ito H, Kurose A, Yamauchi K, Inoue H, Sawai T (2003) Pulmonary lymphangioliomyomatosis: a case report with immunohistochemical details and DNA analysis. *Tohoku J Exp Med* 199(2):119-26
- Phin S, Kupferwasser D, Lam J, Lee-Fruman KK (2003) Mutational analysis of Ribosomal S6 Kinase 2 shows differential regulation of its kinase activity from that of Ribosomal S6 Kinase 1. *Biochem J Pt* [epub ahead of print]
<http://www.biochemj.org/bj/imps/refer.htm?MSID=BJ20021794.htm>
- Plas DR, Thompson CB (2003) Akt Activation Promotes Degradation of Tuberin and FOXO3a via the Proteasome. *J Biol Chem* 278(14):12361-6
- Radimerski T, Montagne J, Rintelen F, Stocker H, van der Kaay J, Downes CP, Hafen E, Thomas G (2002) dS6K-regulated cell growth is dPKB/dPI(3)K-independent, but requires dPDK1. *Nat Cell Biol* 4(3):251-5
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- Satake N, Miyagawa M, Sakurai J, Mitani H, Kobayashi T, Tamura H, Hino O (2002) N-ethyl-N-hydroxyethylnitrosamine (EHEN)-induced renal and hepatocarcinogenesis in the tumor suppressor Tsc2 transgenic rat. *Cancer Lett* 184(2):157-63
- Siegel C (2003) Renal angiomyolipoma: relationships between tumor size, aneurysm formation, and rupture. *J Urol* 169(4):1598-9
- Shiga Y, Tsutsumi M, Suzuki K, Ishikawa S, Shimogama T (2003) Angiomyolipoma with regional lymph node involvement: a case report and literature review. *Hinyokika Kyo* 49(2):81-6
- Soto-Ares G, Joyes B, Lemaitre MP, Vallee L, Pruvo JP (2003) MRI in children with mental retardation. *Pediatr Radiol* 33(5):334-45
- Takahashi N, Kitahara R, Hishimoto Y, Ohguro A, Hashimoto Y, Suzuki T (2003) Malignant transformation of renal angiomyolipoma. *Int J Urol* 10(5):271-273
- Thom M, Harding BN, Lin WR, Martinian L, Cross H, Sisodiya SM (2003) Cajal-Retzius cells, inhibitory interneuronal populations and neuropeptide Y expression in focal cortical dysplasia and microdysgenesis. *Acta Neuropathol (Berl)* 105(6):561-9
- Truong LD, Choi YJ, Shen SS, Ayala G, Amato R, Krishnan B (2003) Renal cystic neoplasms and renal neoplasms associated with cystic renal diseases: pathogenetic and molecular links. *Adv Anat Pathol* 10(3):135-59

Tuna EB, Lebe B, Yorukoglu K (2003) HMB45 and melan-A expression in renal angiomyolipoma and their significance for the diagnosis. *Tumori* 89(1):46-8

Walker CL (2002) Role of hormonal and reproductive factors in the etiology and treatment of uterine leiomyoma. *Recent Prog Horm Res* 57:277-94

Wang L, Rolfe M, Proud CG (2003) Ca²⁺-independent protein kinase C activity is required for alpha 1-adrenergic receptor-mediated regulation of ribosomal protein S6 kinases in adult cardiomyocytes. *Biochem J Pt* [epub ahead of print]
<http://www.biochemj.org/bj/imps/refer.htm?MSID=BJ20030454.htm>

Yeung RS (2002) Tuberous sclerosis as an underlying basis for infantile spasm. *Int Rev Neurobiol* 49:315-32

Yoon HS, Monks TJ, Everitt JI, Walker CL, Lau SS (2002) Cell proliferation is insufficient, but loss of tuberin is necessary, for chemically induced nephrocarcinogenicity. *Am J Physiol Renal Physiol* 283(2):F262-70

TSC TISSUE AVAILABILITY:

The following tissues from individuals with TSC have been received (or will be received in the near future) by the Maryland Brain and Tissue Bank:

- SEGA
- renal tumor
- tuber
- brain from adult with TSC (from autopsy)

Please contact the Brain and Tissue Bank if you are interested in obtaining any of this tissue for your research. You may contact them by phone at: 1-800-847-1539 or via e-mail at btbumab@umaryland.edu

Additional information can be found on their website at:
<http://som1.umaryland.edu/BTBank/main.html>

LEGISLATIVE UPDATE:

The TS Alliance has been instrumental in obtaining congressional support for a \$10 million request for the budget of the Tuberous Sclerosis Complex Research Program in the Congressionally Directed Medical Research Program in the Department of Defense. Updates will be provided as Congress moves forward with their Appropriation hearings.

NEWS:

The Genetics and Public Policy Center is an independent and objective source of information and analysis on genetic technologies and policies. For additional information, and to sign up for updates and the e-newsletter, visit: <http://www.dnapolicy.org>

UPCOMING CONFERENCES:

[Starting with the May 2003 issue, only new conferences will be listed. See previous issues of TSC Alert for complete listing of conferences for 2003. This list will also appear on the TS Alliance website soon as Scientific Conferences/Events.]

May 20-21, 2003

Global Health: A Challenge to Scientists

Natcher Auditorium, Natcher Conference Center (Building 45)

NIH, Bethesda, Maryland

For additional information and to register for the symposium:

<http://www.fic.nih.gov/35th/35thsymposium.html>

May 21, 2003

IBM's Life Sciences Seminar: Data Management and Integration Issues in Drug Discovery

Marriott Residence Inn

Bethesda, MD

Enroll online at: <http://www.ibm.com/solutions/LSevents1> or call 1-800-426-0889, option #2 for enrollment. Mention Code Y-7565

July 23-24, 2003

From Genome to Disease: A Symposium of High Throughput Biology

Natcher Auditorium, Natcher Conference Center (Building 45)

NHLBI, NIH, Bethesda, MD

For additional information and to register for the symposium:

<http://www.nhlbi.nih.gov/meetings/pga/index.htm>

September 18-20, 2003

Adolescent Brain Development: Vulnerabilities and Opportunities

New York City

Jointly sponsored by the New York Academy of Sciences, Science and Technology Meetings Program, and the University of Pittsburgh School of Medicine, Center for Continuing Education

Contact for information and deadlines: New York Academy of Sciences;

T: 212.838.0230 x 324; E: conference@nyas.org;

For complete details visit: <http://www.nyas.org/scitech/conf/adolbrain.cfm>

October 1-4, 2003

Child Neurology Society Meeting

Includes a one-day symposium on Tuberous Sclerosis Complex on Wednesday, October 1

Miami Beach, FL

http://www.childneurologysociety.org/events/evt_001.asp

November 8-12, 2003

Society for Neuroscience

New Orleans, LA

Abstract Submission Deadlines:

May 5, 2003 (print submission)

May 19, 2003 (online submission)

<http://apu.sfn.org/ACSplash.cfm>

September 16-18, 2004

Tuberous Sclerosis Association International Research Conference

Queens College, Cambridge UK (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 – Coming Soon!

<http://www.tsalliance.org>