



TSC ALERT

Edited by Vicky H Whittemore, PhD

November 2006

Welcome to the November 2006 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 2006 *TSC Alert* contact: vwhittemore@tsalliance.org

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SAVE THE DATE

May 24-26, 2007

Tuberous Sclerosis Complex International Research Conference 2007 in Rome (Italy)

Venue: Grand Hotel Palazzo Carpegna, Rome, Italy

Information: <http://www.ptsroma.it/tsc2007/>

September 23-25, 2007

Tuberous Sclerosis Complex: From Genes to New Therapeutics

International TSC Conference organized by the Tuberous Sclerosis Alliance

Loews Annapolis Hotel, Annapolis, MD

More information coming soon!

September 11-14, 2008

International TSC Conference

Organized by the Tuberous Sclerosis Association, U.K.

Brighton, U.K.

More information coming soon!

REQUEST FOR INFORMATION

Public Comment Requested on Genome-Wide Association Studies

The NIH is interested in advancing Genome-Wide Association Studies (GWAS) to identify common genetic factors that influence health and disease because the information derived from such studies will be essential for developing new approaches to reduce disease burden and promote health. GWAS are currently defined as any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition. The goal of the proposed policy is to advance science for the benefit of the public through the creation of a centralized NIH GWAS data repository. Comments may be submitted through November 30, 2006. Go to the following web site:

<http://grants.nih.gov/grants/gwas/index.htm>

Request for Information (RFI): To Solicit Input and Ideas for Roadmap Trans-NIH Strategic Initiatives

The NIH is seeking input from the scientific community, health professionals, patient advocates, and the general public about innovative and cross-cutting initiatives that will improve and accelerate biomedical research and its impact on the health of the Nation. Collecting these ideas is an initial step in the process of identifying a new cohort of "Roadmap" trans-NIH strategic initiatives for Fiscal Year 2008. This idea-gathering phase has also included obtaining input from scientist consultants and the NIH Institutes and Centers. This RFI provides an opportunity for respondents to submit their own ideas and to view ideas nominated to date. The NIH expects to spend \$30 - 50 million per year from within the currently projected Roadmap budget for approximately 5-8 new 5-year (or in exceptional cases up to 10-year) initiatives. For more information, go to:

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-011.html>

FUNDING OPPORTUNITIES

Understanding and Treating Tuberous Sclerosis Complex (R01) (PAS-06-205)

National Institute of Neurological Disorders and Stroke

National Cancer Institute

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Mental Health

Tuberous Sclerosis Alliance

Application Receipt/Submission Date(s): Multiple dates, see announcement.

<http://grants.nih.gov/grants/guide/pa-files/PAS-06-205.html>

Understanding and Treating Tuberous Sclerosis Complex (R21) (PAS-06-206)

National Institute of Neurological Disorders and Stroke

National Cancer Institute

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Mental Health

Tuberous Sclerosis Alliance

Application Receipt/Submission Date(s): Multiple dates, see announcement.

<http://grants.nih.gov/grants/guide/pa-files/PAS-06-206.html>

Pathway to Independence Awards

National Institutes of Health

The NIH Pathway to Independence Award is an innovative, new program that will provide an opportunity for promising postdoctoral scientists to receive both

mentored and independent research support from the same award. NIH plans to issue between 150 and 200 awards for this program in the first year, and for the each of the next five years, amounting to approximately \$390 million. The actual number and distribution of awards made by the NIH Institutes and Centers will depend upon the quality of the applications received and the results of the scientific peer review process. The same standard submission dates for research career development awards will be used, please see <http://grants.nih.gov/grants/funding/submissionschedule.htm> for details. For more information about this award, see: http://grants.nih.gov/grants/new_investigators/pathway_independence.htm

NHGRI Fellowships

The National Human Genome Research Institute, National Institutes of Health, is offering individual fellowships to highly qualified students and scientists who are seeking training that will enable them to engage in research relevant to the Human Genome Project. Training of scholars in examining the ethical, legal and social implications of human genome research is also encouraged, but is not available for pre-doctoral students.

Three types of fellowships are offered:

1. Postdoctoral fellowships for individuals who have received their doctoral degree within the last seven years. The application receipt dates are December 5, 2006, April 8, 2007 and August 8, 2007.
2. Senior postdoctoral fellowships for individuals who received their doctoral degree more than seven years ago. The application receipt dates are December 5, 2006, April 8, 2007 and August 8, 2007.
3. Pre-doctoral Minority fellowships for graduate students with disabilities and underrepresented minority graduate students to pursue a doctoral degree. There has been no change in the application receipt dates of these applications. The standard application receipt dates are November 15 and May 1.

Fellowship support is provided through the National Research Service Award. Only U.S. citizens or permanent residents of the United States are eligible to apply.

For additional information about fellowship opportunities available through the NHGRI, please visit our home page at: <http://www.genome.gov/10000950>.

You may also contact the following staff:

Individual and Senior Postdoctoral Fellowships and Minority Pre-Doctoral Fellowships in Genomic Analysis and Technology:

Bettie J. Graham, Ph.D.
TEL: (301) 496-7531
e-mail: bettie_graham@nih.gov

Individual and Senior Postdoctoral Fellowships in ELSI Topics:
Elizabeth Thomson, M.S., R.N.
TEL: (301) 402-4997
e-mail: elizabeth_thomson@nih.gov

For information about PHS Grant Policy, applicants may contact:

Ms. Cheryl Chick
TEL: (301) 402-0733
E-mail: cheryl_chick@nih.gov

2007 NIH Director's Pioneer Award Program (DP1)

The NIH Director's Pioneer Award Program (NDPA) is meant to complement NIH's traditional, investigator-initiated grant programs by supporting individual scientists of exceptional creativity who propose pioneering approaches to major contemporary challenges in biomedical and behavioral research.

The National Institutes of Health (NIH) is engaged in a series of initiatives, collectively known as the "NIH Roadmap for Medical Research" (<http://nihroadmap.nih.gov>), which promotes clinical and translational investigation and aim to improve health and prevent disease. The NIH Director's Pioneer Award Program, is a [High-Risk Research](#) initiative of [Research Teams of the Future](#).

For more information regarding the NIH Director's Pioneer Award Program, visit: <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-005.html>

Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences (R21) (RFA-RM-07-004)

NIH Roadmap Initiatives
Application Receipt Date(s): February 23, 2007
<http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-004.html>

International Research Scientist Development Award (IRSDA) [K01] (PAR-07-014)

John E. Fogarty International Center
Office of Dietary Supplements
Application Receipt/Submission Date(s): January 16, 2007; January 16, 2008; January 16, 2009
<http://grants.nih.gov/grants/guide/pa-files/PAR-07-014.html>

Herbert H. Jasper Postdoctoral Research Fellowship

This fellowship provides a two-year stipend and travel allowance to undertake a postdoctoral research project within the Groupe de Recherche sur le Système Nerveux Central (GRSNC) of the University of Montreal. The application deadline is Jan. 31, 2007. For more information, call (514) 343-6366 or write to grsnc@umontreal.ca

AAAS Science and Technology Policy Fellowships

The American Association for the Advancement of Science offers fellowships that help to establish and nurture links between federal decision-makers and scientific professionals. The application deadline for 2007-08 fellowships is Dec. 20, 2006. For more information, visit <http://fellowships.aaas.org>

NEW TSC PUBLICATIONS

Arsham AM, Neufeld TP (2006) Thinking globally and acting locally with TOR. *Curr Opin Cell Biol* 2006 Oct 11 [Epub ahead of print]

- Atallah D, Checrallah A, Rouzier R, Ghossain MA, Chahine G (2006) Retroperitoneal lymphangioliomyoma mimicking ovarian tumor emerging after tamoxifen therapy. *Obstet Gynecol* 108(3 Pt 2):762-4
- Avruch J, Hara K, Lin Y, Liu M, Long X, Ortiz-Vega S, Yonezawa K (2006) Insulin and amino-acid regulation of mTOR signaling and kinase activity through the Rheb GTPase. *Oncogene* 25(48):6361-72
- Baba M, Hong SB, Sharma N, Warren MB, Nickerson ML, Iwamatsu A, Esposito D, Gillette WK, Hopkins RF 3rd, Hartley JL, Furihata M, Oishi S, Zhen W, Burke TR Jr, Linehan WM, Schmidt LS, Zhar B (2006) Folliculin encoded by the BHD gene interacts with a binding protein, FNIP1, and AMPK, and is involved in AMPK and mTOR signaling. *Proc Natl Acad Sci U S A* 103(42):15552-7 [Epub 2006 Oct 6]
- Binder DK, Steinhauser C (2006) Functional changes in astroglial cells in epilepsy. *Glia* 54(5):358-68
- Cao Y, Kamioka Y, Yokoi N, Kobayashi T, Hino O, Onodera M, Mochizuki N, Nakae J (2006) Interaction of FoxO1 and TSC2 induces insulin resistance through activation of mTOR/p70S6K pathway. *J Biol Chem* 2006 Oct 31 [Epub ahead of print]
- Chano T, Saji M, Inoue H, Minami K, Kobayashi T, Hino O, Okabe H (2006) Neuromuscular abundance of RB1CC1 contributes to the non-proliferating enlarged cell phenotype through both RB1 maintenance and TSC1 degradation. *Int J Mol Med* 18(3):425-32
- Debloom JR, Friedrichs A, Swick BL, Whitaker DC (2006) Management of cutaneous angiomyolipoma and its association with tuberous sclerosis. *J Dermatol* 33(11):783-6
- de Carvalho Neto A, Gasparetto EL, Bruck I (2006) Subependymal giant cell astrocytoma with high choline/creatine ratio on proton MR spectroscopy. *Arq Neuropsiquiatr* 64(3B):877-80
- dos Santos ML, Mattos e Dinato SL, Moraes JM, Nakanishi CP, Mattos e Dinato M (2006) [Familial clinical manifestation in patients with neuromesoectodermic defect.] *Arq Neuropsiquiatr* 64(3B):798-801 [Article in Portuguese]
- Gan B, Peng X, Nagy T, Alcaraz A, Gu H, Guan JL (2006) Role of FIP200 in cardiac and liver development and its regulation of TNF{alpha} and TSC-mTOR signaling pathways. *J Cell Biol* 2006 Oct 2 [Epub ahead of print]
- Ho TB, Hull JH, Hughes NC (2006) An 86-year-old female with lymphangioliomyomatosis. *Eur Respir J* 28(5):1065-4
- Inci O, Kaplan M, Yalcin O, Atakan IH, Kubat H (2006) Renal angiomyolipoma with malignant transformation, simultaneous occurrence with malignancy and other complex clinical situations. *Int Urol Nephrol* 2006 Oct 10 [Epub ahead of print]
- Jozwiak J, Kotulska K, Grajkowska W, Jozwiak S, Zalewski W, Oldak M, Lojek M, Rainko K, Maksym R, Lazarczyk M, Skopinski P, Wlodarski P (2006) Upregulation of the WNT pathway in tuberous sclerosis-associated subependymal giant cell astrocytomas. *Brain Dev* 2006 Oct 26 [Epub ahead of print]
- Juvet SC, Hwang D, Downey GP (2006) Rare lung diseases I – Lymphangioliomyomatosis. *Can Respir J* 13(7):375-80
- Lin CC, Lee TC, Liu KL, Lin JT, Lin MT, Wang HP (2006) Gastrointestinal: Lymphangioliomyomatosis with protein-losing enteropathy. *J Gastroenterol Hepatol* 21(12):1860

- Maeda M, Hino O (2006) Molecular tumor markers for asbestos-related mesothelioma: Serum diagnostic markers. *Pathol Int* 56(11):649-54
- Marcotte L, Crino PB (2006) The neurobiology of the tuberous sclerosis complex. *Neuromolecular Med* 8(4):531-46
- Overby PJ, Kossoff EH (2006) Treatment of infantile spasms. *Curr Treat Options Neurol* 8(6):457-64
- Pantuck AJ, Thomas G, Belldegrun AS, Figlin RA (2006) Mammalian target of rapamycin inhibitors in renal cell carcinoma: current status and future applications. *Semin Oncol* 33(5):607-13
- Pollock-Barziv SM, Cohen MM, Downey GP, Johnson SR, Sullivan E, McCormack FX (2006) Air travel in women with Lymphangiomyomatosis. *Thorax* 2006 Oct 13 [Epub ahead of print]
- Raft J, Lalot JM, Meistelman C, Longrois D (2006) [Renal angiomyolipoma rupture during pregnancy.] *Gynecol Obstet Fertil* 34(10):917-9 [Epub 2006 Sep 25] [Article in French]
- Rice JM (2006) Inducible and transmissible genetic events and pediatric tumors of the nervous system. *J Radiat Res (Tokyo)* 47 Suppl B:B1-B11
- Rosen N, She QB (2006) AKT and cancer--is it all mTOR? *Cancer Cell* 10(4):254-6
- Rothberg BE, Grooms MC, Dharnidkarka VR (2006) Rapid Growth of a Kidney Angiomyolipoma After Initiation of Oral Contraceptive Therapy. *Obstet Gynecol* 108(3 Pt 2):734-736
- Schick V, Majores M, Engels G, Spitoni S, Koch A, Elger CE, Simon M, Knobbe C, Blumcke I, Becker AJ (2006) Activation of Akt independent of PTEN and CTMP tumor-suppressor gene mutations in epilepsy-associated Taylor-type focal cortical dysplasias. *Acta Neuropathol (Berl)* 2006 Sep 30 [Epub ahead of print]
- Seyama K, Kumasaka T, Souma S, Sato T, Kurihara M, Mitani K, Tominaga S, Fukuchi Y (2006) Vascular endothelial growth factor-D is increased in serum of patients with lymphangiomyomatosis. *Lymphat Res Biol* 4(3):143-52
- Tai HC, Lin JW, Wang YH, Eng HL, Lu HI, Liu YW, Huang CC (2006) Pulmonary lymphangiomyomatosis followed by a localized retroperitoneal lymphangiomyoma. *APMIS* 114(11):821-4
- Taveira-Dasilva AM, Steagall WK, Moss J (2006) Lymphangiomyomatosis. *Cancer Control* 13(4):276-85
- Toyoda K, Matsumoto K, Inoue H, Komori M, Fujita M, Hashimoto S, Kuwano K, Nakanishi Y (2006) A pregnant woman with complications of lymphangiomyomatosis and idiopathic thrombocytopenic purpura. *Intern Med* 45(19):1097-100 [Epub 2006 Nov 1]
- Tschuluun N, Wenzel HJ, Schwartzkroin PA (2006) Irradiation exacerbates cortical cytopathology in the Eker rat model of tuberous sclerosis complex, but does not induce hyperexcitability. *Epilepsy Res* 2006 Sep 28 [Epub ahead of print]
- Wang H, Kubica N, Ellisen LW, Jefferson LS, Kimball SR (2006) Dexamethasone represses signaling through the mammalian target of rapamycin in muscle cells by enhancing expression of REDD1. *J Biol Chem* 2006 Oct 30 [Epub ahead of print]
- Yang Q, Inoki K, Ikenoue T, Guan KL (2006) Identification of Sin1 as an essential TORC2 component required for complex formation and kinase activity. *Genes Dev* 20(20):2820-32

Yu J, Henske EP (2006) Estrogen-Induced Activation of Mammalian Target of Rapamycin Is Mediated via Tuberin and the Small GTPase Ras Homologue Enriched in Brain. *Cancer Res* 66(19):9461-6

Zhang HH, Lipovsky AI, Dibble CC, Sahin M, Manning BD (2006) S6K1 Regulates GSK3 under Conditions of mTOR-Dependent Feedback Inhibition of Akt. *Mol Cell* 24(2):185-97

Zhao XY, Yang S, Zhou HL, Zhu YG, Wei L, Du WH, Ren YQ, Liang YH, Hou YX, Chen JJ, Zhang XJ (2006) Two novel TSC2 mutations in Chinese patients with tuberous sclerosis complex and a literature review of 20 patients reported in China. *Br J Dermatol* 155(5):1070-3

CONFERENCES & SEMINARS

November 30, 2006

TSC/LAM Seminar Series

LAM Research: New Insights and Unanswered Questions

Presenter: Joel Moss, M.D., Ph.D; Discussants: Miles Brown, M.D.; George Demetri, M.D.
Harvard Medical School, 5:00 – 7:00 PM

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

December 1-5, 2006

2006 AES Annual Meeting/North American Regional Epilepsy Congress

San Diego Convention Center

For more information: <http://www.aesnet.org/Visitors/AnnualMeeting/index.cfm>

****Investigator's Workshop: Molecular and Cellular Alterations in TSC: Functional Implications; Saturday, December 2, 2006 from 8:30 – 10:00 AM**

****TSC Special Interest Group; Saturday, December 2, 2006 from 3:00 – 4:30 PM**

****Stop by the TS Alliance Exhibit in the Exhibit Hall**

December 5, 2006

1 pm PT/4 pm ET (Teleconference Series)

Understanding your MRI Report: A Guide for Brain Tumor Patients

Presenter: Philip Gutin, M.D., Chief, Neurosurgical Service and Fred Lebow, Chair in Neuro-oncology, Memorial Sloan-Kettering Cancer Center

Sponsors: National Brain Tumor Foundation

To register, visit www.brainumor.org and fill out the online form or call 1-800-934-2873

February 1-2, 2007

National Coalition for Health Professional Education in Genetics (NCHPEG) and Genetics Resources on the Web (GROW) 10th Annual Meeting: Pharmacogenomics

Hyatt Regency Bethesda, Bethesda, MD

Abstract deadline: October 6, 2006

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

March 29-30, 2007

Curing Epilepsy 2007: Translating Discoveries into Therapies

Natcher Conference Center, Bethesda, MD

Follow-up to 2000 Conference "Curing Epilepsy: Focus on the Future"

<http://www.ninds.nih.gov>

April 19-22, 2007

2007 LAM International Research Conference

The LAM Foundation

Cincinnati, OH

<http://www.thelamfoundation.org>

May 9-12, 2007

68th Annual Meeting of the Society for Investigative Dermatology

The Century Plaza Hotel, Los Angeles, CA

For more information: www.sidnet.org

May 24-26, 2007

Tuberous Sclerosis Complex International Research Conference 2007 in Rome (Italy)

Venue: Grand Hotel Palazzo Carpegna, Rome, Italy

Information: <http://www.ptsroma.it/tsc2007/>

September 23-25, 2007

Tuberous Sclerosis Complex: From Genes to New Therapeutics

International TSC Research Symposium organized by the Tuberous Sclerosis Alliance

Loews Annapolis Hotel, Annapolis, MD

More information coming soon on the TS Alliance website at www.tsalliance.org

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Brighton, U.K.

More information coming soon!

NEWS

TS Alliance Launches TSC Natural History Database in Minnesota

The TS Alliance is happy to announce that the TSC Natural History Database has been launched at the TSC Clinic Without Walls at the Minnesota Epilepsy Group in St. Paul, MN under the direction of Michael Frost, M.D., Director of the TSC Clinic. Dr. Frost and his group will participate in the six-month pilot phase of the project together with Steven Sparagana, M.D. and the TSC Clinic at Texas Scottish Rite Hospital in Dallas. After the pilot phase, additional TSC Clinics will be added to the database project until all of the sites are collecting data for the project.

Researchers Identify a Key Regulator for Skin Stem Cells

By turning on a single gene, researchers can prevent skin stem cells from maturing into the three types of adult skin cells -- epidermal, sebaceous and hair cells. They say this finding could have important implications for scientists trying to grow stem cells in the lab, for both research and potential therapies. This research was published by Elaine Fuchs, Ph.D., HHMI investigator, The Rockefeller University, in the October 06, 2006, issue of Cell. For the full story, go to:

<http://www.hhmi.org/news/fuchs20061006.html>

Map Helps Explain Alternative Splicing in the Brain

Combining data from years of laboratory work with the power of bioinformatics, HHMI researchers have created a map that helps explain how the brain generates the assortment of specialized proteins it needs to process information. This research was published in the October 25, 2006, issue of Nature by Robert B. Darnell, M.D., Ph.D., HHMI investigator at The Rockefeller University. For the full story, go to: <http://www.hhmi.org/news/darnell20061025.html>

TSC CLINICAL TRIALS AND STUDIES

1. Sirolimus in Treating Patients with Angiomyolipoma of the Kidney

Official Title: Phase II Study of Sirolimus in Patients with Angiomyolipoma of the Kidney Secondary to Tuberous Sclerosis or Lymphangiomyomatosis

Study Purpose:

Rationale: Drugs used in chemotherapy, such as sirolimus, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing.

Purpose: This phase II trial is studying how well sirolimus works in treating individuals with angiomyolipoma of the kidney.

Eligibility:

Ages Eligible for Study: 18 Years - 65 Years

Genders Eligible for Study: Both

Location and Contact Information:

Please refer to this study by ClinicalTrials.gov identifier NCT00126672

Connecticut

Connecticut Children's Medical Center, Hartford, Connecticut, 06106, United States; Recruiting
Francis J. DiMario, MD 860-545-9460

Massachusetts

Massachusetts General Hospital, Boston, Massachusetts, 02114, United States; Recruiting
Elizabeth Thiele, MD, PhD 617-726-6540

New York

New York University Medical Center, New York, New York, 10016, United States; Recruiting
Daniel K. Miles, MD 212-263-8318

Ohio

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, 45229-3039, United States; Recruiting
David Franz, MD 513-636-4222 david.franz@chmcc.org

Pennsylvania

University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, 19104-4283, United States; Recruiting
Peter Crino, MD, PhD 215-349-5312

Texas

University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, 75390, United States; Recruiting
Arthur I. Sagalowsky, MD 214-645-8797 arthur.sagalowsky@utsouthwestern.edu

Study chairs or principal investigators: Sandra Dabora, MD, PhD, Study Chair, Brigham and Women's Hospital

For more information about this clinical trial, visit:

<http://www.cancer.gov/clinicaltrials/DFCI-04298>

2. Siblings Wanted for a Modifier Gene Research Study



The Herscot Center for Tuberous Sclerosis Complex and the Center for Human Genetic Research at the Massachusetts General Hospital are trying to identify additional genes that play a role in neurological problems in TSC.

We would like to enroll TSC siblings over 2 years of age that differ in their expression of
autism or **infantile spasms** or **uncontrollable seizures**

Participants will have:

- clinical evaluation by a neurologist specialized in TSC (Dr. Elizabeth Thiele)
- blood drawn
- brain MRI
- EEG
- neuropsychological testing (only for siblings differing in autism)

The whole study will take about 2 days to complete. There is no direct cost to the participants.

Travel and lodging will be reimbursed for participants who live more than 2 hours away from Boston.

For more information contact Susana Camposano 617-726 0240 (M-F, 8-5),
scamposano@partners.org

3. TSC and TSC/LAM protocols. Our Clinical Research Nurses can be reached toll-free at 1-877-NIH-LUNG, # 3 on the menu or locally through 301-496-3632.

TSC INFORMATION

For information about TSC and the Tuberous Sclerosis Alliance, visit the TS Alliance Web site at: <http://www.tsalliance.org> or contact the TS Alliance at info@tsalliance.org or by telephone: 1-800-225-6872 or 301-562-9890.