



TSC ALERT

Edited by Vicky H Whittemore, PhD

November 2005

Welcome to the November 2005 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 2005 *TSC Alert* contact: vwhittemore@tsalliance.org

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GRANT ANNOUNCEMENTS

UNDERSTANDING AND TREATING TUBEROUS SCLEROSIS COMPLEX

Participating Organizations

National Institutes of Health (NIH), (<http://www.nih.gov/>)

Tuberous Sclerosis Alliance (TS Alliance), (<http://www.tsalliance.org>)

Components of Participating Organizations

National Institute of Neurological Disorders and Stroke (NINDS), (<http://www.ninds.nih.gov>)

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), (<http://www.niddk.nih.gov/>)

National Institute of Mental Health (NIMH), (<http://www.nimh.nih.gov>)

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), (<http://www.niams.nih.gov>)

National Cancer Institute (NCI), (<http://www.nci.nih.gov>)

Letters of Intent Receipt Date(s): Not Applicable

Application Receipt Dates(s): Standard dates apply, please see <http://grants.nih.gov/grants/funding/submissionschedule.htm> for details

Peer Review Date(s): Standard dates apply, please see <http://grants.nih.gov/grants/funding/submissionschedule.htm> for details

Council Review Date(s): Standard dates apply, please see <http://grants.nih.gov/grants/funding/submissionschedule.htm> for details

Earliest Anticipated Start Date: April 2006

Additional Information To Be Available Date (Url Activation Date): Not Applicable

Expiration Date: March 2, 2008

PLANNING GRANTS FOR INSTITUTIONAL CLINICAL AND TRANSLATIONAL SCIENCE AWARDS (RFA-RM-06-001)

NIH Roadmap Initiatives

National Center for Research Resources

Application Receipt Date(s): March 27, 2006

<http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-06-001.html>

INSTITUTIONAL CLINICAL AND TRANSLATIONAL SCIENCE AWARD (RFA-RM-06-002)

NIH Roadmap Initiatives

National Center for Research Resources

Application Receipt Date(s): March 27, 2006

<http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-06-002.html>

NIDDK CAREER TRANSITION AWARD (K22) IN PATIENT-ORIENTED RESEARCH (PAR-06-002)

National Institute of Diabetes and Digestive and Kidney Diseases

Office of Dietary Supplements

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

<http://grants.nih.gov/grants/guide/pa-files/PAR-06-002.html>

DEVELOPMENT OF RECOMBINASE-EXPRESSING ("Driver") MOUSE LINES FOR STUDYING THE NERVOUS SYSTEM (U01)(RFA-MH-06-007)

NIH Blueprint for Neuroscience Research

National Institute of Mental Health

National Center for Complementary and Alternative Medicine

National Center for Research Resources

National Eye Institute

National Institute on Aging

National Institute on Alcohol Abuse and Alcoholism

National Institute of Biomedical Imaging and Engineering

National Institute of Child Health and Human Development

National Institute on Drug Abuse

National Institute on Deafness and Other Communication Disorders

National Institute of Dental and Craniofacial Research

National Institute of Environmental Health Sciences

National Institute of General Medical Sciences

National Institute of Neurological Disorders and Stroke

National Institute of Nursing Research

Application Receipt Date(s): January 19, 2006

<http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-06-007.html>

NIH DIRECTOR'S PIONEER AWARD PROGRAM (DP1)(RFA-RM-06-005)

NIH Roadmap Initiatives

Application Receipt Date(s): February 27, 2006

<http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-06-005.html>

INTERNATIONAL CLINICAL, OPERATIONAL AND HEALTH SERVICES RESEARCH TRAINING AWARD (ICOHRTA) [D43](RFA-TW-06-002)

John E. Fogarty International Center

National Institute on Aging

National Institute on Drug Abuse

National Institute of Dental and Craniofacial Research

National Institute of Mental Health

National Institute of Neurological Disorders and Stroke

Office of Dietary Supplements

Application Receipt Date(s): January 25, 2006

<http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-06-002.html>

SMALL GRANT PROGRAM FOR CONFERENCE SUPPORT (R13)(PA-06-074)

Agency for Healthcare Research and Quality
Office of Extramural Research, Education, and Priority Populations
Application Receipt Date(s): December 20, February 20, April 20, June 20
August 20, October 20, annually (beginning December 20, 2005 and ending
October 20, 2008)
<http://grants.nih.gov/grants/guide/pa-files/PA-06-074.html>

PROTEIN INTERACTIONS GOVERNING MEMBRANE TRANSPORT IN PULMONARY HEALTH AND DISEASE (R01)(PA-06-076)

National Heart, Lung, and Blood Institute
Application Receipt Date(s): Multiple dates, see announcement.
<http://grants.nih.gov/grants/guide/pa-files/PA-06-076.html>

RESEARCH ON CLINICAL DECISION MAKING IN LIFE-THREATENING ILLNESS (R01)(PA-06-077)

National Institute of Nursing Research
National Cancer Institute
Application Receipt Date(s): Multiple dates, see announcement.
<http://grants.nih.gov/grants/guide/pa-files/PA-06-077.html>

DISSEMINATION AND IMPLEMENTATION RESEARCH IN HEALTH (R03)(PAR-06-071)

National Institute of Mental Health
National Cancer Institute
National Institute on Alcohol Abuse and Alcoholism
National Institute on Drug Abuse
National Institute on Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Nursing Research
Office of Behavioral and Social Science Research
Office of Dietary Supplements
Application Receipt Date(s): Multiple dates, see announcement.
<http://grants.nih.gov/grants/guide/pa-files/PAR-06-071.html>

DISSEMINATION AND IMPLEMENTATION RESEARCH IN HEALTH (R21)(PAR-06-072)

National Institute of Mental Health
National Cancer Institute
National Institute on Alcohol Abuse and Alcoholism
National Institute on Drug Abuse
National Institute on Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Nursing Research
Office of Behavioral and Social Science
Research Office of Dietary Supplements
Application Receipt Date(s): Multiple dates, see announcement.
<http://grants.nih.gov/grants/guide/pa-files/PAR-06-072.html>

JAMES S. McDONNELL FOUNDATION: 21st Century Science Initiative - 2006

Research Award Application Deadline: 5:59 PM CST on Monday March 13, 2006

The James S. McDonnell Foundation (JSMF) announces updated program descriptions and application guidelines for its 21st Century Science Initiative Research Awards. The 21st Century Research Awards support investigator-initiated research. Funding is available for research projects in Brain Cancer; Bridging Brain, Mind, and Behavior; and Studying Complex Systems. Program information, application guidelines, and proposal preparation instructions are available at: <http://www.jsmf.org> No geographic restrictions; international applications are encouraged. Information on the Foundation's 21st Century Collaborative Activity Awards is also available on the website. Thank you for your interest.

AVAILABILITY OF DELTAGEN AND LEXICON GENETICS KNOCK OUT MICE AND PHENOTYPIC DATA (NOT-OD-06-012)

National Institutes of Health

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-012.html>

NEW TSC PUBLICATIONS

Altomare DA, Testa JR (2005) Perturbations of the AKT signaling pathway in human cancer. *Oncogene* 24(50):7455-64

Astrinidis A, Henske EP (2005) Tuberous sclerosis complex: linking growth and energy signaling pathways with human disease. *Oncogene* 24(50):7475-7481

Coffey VG, Zhong Z, Shield A, Canny BJ, Chibalin AV, Zierath JR, Hawley JA (2005) Early signaling responses to divergent exercise stimuli in skeletal muscle from well-trained humans. *FASEB J* 2005 Nov 2 [Epub ahead of print]

Del Sordo R, Colella R, Leite S, Sidoni A (2005) [Cutaneous angiomyolipoma: a case report and literature review] *Pathologica* 97(3):137-40 [Article in Italian]

Ellisen LW (2005) Growth Control Under Stress: mTOR Regulation through the REDD1-TSC Pathway. *Cell Cycle* 2005 Nov 1 4(11) [Epub ahead of print]

Ewalt DH, Diamond N, Rees C, Sparagana SP, Delgado M, Batchelor L, Roach ES (2005) Long-term outcome of transcatheter embolization of renal angiomyolipomas due to tuberous sclerosis complex. *J Urol* 174(5):1764-1766

Ganame J, D'hooge J, Mertens L (2005) Different deformation patterns in intracardiac tumors. *Eur J Echocardiogr* 6(6):461-464 Epub 2005 Apr 2

Houben MP, van Duijn CM, Coebergh JW, Tijssen CC (2005) [Gliomas: the role of environmental risk factors and genetic predisposition.] *Ned Tijdschr Geneesk* 149(41):2268-72 [Article in Dutch]

Ichikawa T, Wakisaka A, Daido S, Takao S, Tamiya T, Date I, Koizumi S, Niida Y (2005) A Case of Solitary Subependymal Giant Cell Astrocytoma: Two Somatic Hits of TSC2 in the Tumor, without Evidence of Somatic Mosaicism. *J Mol Diagn* 7(4):544-9

Kataoka K, Fujimoto K, Ito D, Koizumi M, Toyoda E, Mori T, Kami K, Doi R (2005) Expression and prognostic value of tuberous sclerosis complex 2 gene product tuberin in human pancreatic cancer. *Surgery* 138(3):450-5

Kwiatkowski DJ, Manning BD (2005) Tuberous sclerosis: a GAP at the crossroads of multiple signaling pathways. *Hum Mol Genet* 14 Spec No. 2:R251-8

Majores M, Schick V, Engels G, Fassunke J, Elger CE, Schramm J, Blumcke I, Becker AJ (2005) Mutational and immunohistochemical analysis of ezrin-, radixin-, moesin (ERM) molecules in epilepsy-associated glioneuronal lesions. *Acta Neuropathol (Berl)* 2005 Oct 18 [Epub ahead of print]

Malanchuk OM, Pozur V, Panasyuk GG, Nemazanyy IO, Filonenko VV, Gout IT, Palchevskyy SS (2005) Identification of novel binding partners for tuberous sclerosis complex 2 (TSC2) by yeast two-hybrid approach. *Exp Oncol* 27(3):186-90

Mennel S, Meyer CH, Eggarter F, Peter S (2005) Autofluorescence and angiographic findings of retinal astrocytic hamartomas in tuberous sclerosis. *Ophthalmologica* 219(6):350-6

- Mhanna T, Ranchere-Vince D, Hervieu V, Tardieu D, Scoazec JY, Partensky C (2005) Clear cell myomelanocytic tumor (PEComa) of the duodenum in a child with a history of neuroblastoma. *Arch Pathol Lab Med* 129(11):1484-6
- Mullerad M, Hidas G, Kastin A, Issaq E, Moskovitz B, Nativ O (2005) [Nephron sparing surgery as a treatment modality for renal angiomyolipoma.] *Harefuah* 144(9):619-21, 678, 677 [Article in Hebrew]
- Musse L (2005) Tuberous sclerosis complex. *Dermatol Nurs* 17(5):376, 380
- Nellist M, Sancak O, Goedbloed MA, Veghel-Plandsoen MV, Maat-Kievit A, Lindhout D, Eussen BH, De Klein A, Halley DJ, Ouweland AM (2005) Large Deletion at the TSC1 Locus in a Family with Tuberous Sclerosis Complex. *Genet Test* 9(3):226-30
- Pinto Gama HP, de Rocha AJ, Braga FT, da Silva CJ, Martins Maia AC Jr, de Campos Meirelles RG, Mendoca de Rego JI, Lederman HM (2005) Comparative analysis of MR sequences to detect structural brain lesions in tuberous sclerosis. *Pediatr Radiol* 2005 Nov 11;1-7 [Epub ahead of print]
- Raft J, Lalot JM, Meistelman C, Longrois D (2005) Influence of pregnancy on renal angiomyolipoma.] *Gynecol Obstet Fertil* [Epub ahead of print] [Article in French]
- Sarbassov dos D, Ali SM, Sabatini DM (2005) Growing roles for the mTOR pathway. *Curr Opin Cell Biol* 17(6):596-603 Epub 2005 Oct 13
- Sekiguchi G (2005) [Dental enamel pitting in tuberous sclerosis complex.] *No To Hattatsu* 37(6):512-6. [Article in Japanese]
- Sudeep K, John M (2005) Acute abdominal pain and palpable mass. Tuberous sclerosis. *N Z Med J* 118(1223):U1692
- Sundaram SK, Chugani HT, Chugani C (2005) Positron emission tomography methods with potential for increased understanding of mental retardation and developmental disabilities. *Ment Retard Dev Disabil Res Rev* 2005 Oct 20 11(4):325-330 [Epub ahead of print]
- Tavazoie SF, Alvarez VA, Ridenour DA, Kwiatkowski DJ, Sabatini BL (2005) Regulation of neuronal morphology and function by the tumor suppressors Tsc1 and Tsc2. *Nat Neurosci* 2005 Nov 6 [Epub ahead of print]
- Urano J, Comiso MJ, Guo L, Aspuria PJ, Deniskin R, Tabancay AP Jr, Kato-Stankiewicz J, Tamanoi F (2005) Identification of novel single amino acid changes that result in hyperactivation of the unique GTPase, Rheb, in fission yeast. *Mol Microbiol* 58(4):1074-86
- Venugopalan P, Babu JS, Al-Bulushi A (2005) Right atrial rhabdomyoma acting as the substrate for Wolff-Parkinson-White syndrome in a 3-month-old infant. *Acta Cardiol* 60(5):543-5
- Waltereit R, Welzl H, Dichgans J, Lipp HP, Schmidt WJ, Weller M (2005) Enhanced episodic-like memory and kindling epilepsy in a rat model of tuberous sclerosis. *J Neurochem*. 2005 Nov 21 [Epub ahead of print]
- Wilson C, Idziaszczyk S, Colley J, Humphreys V, Guy C, Maynard J, Sampson JR, Cheadle JP (2005) Induction of Renal Tumorigenesis with Elevated Levels of Somatic Loss of Heterozygosity in Tsc1+/- Mice on a Blm-Deficient Background. *Cancer Res* 65(22):10179-10182
- Wong M (2005) Advances in the pathophysiology of developmental epilepsies. *Semin Pediatr Neurol* 12(2):72-87
- Xiao Z, Xiang J, Holowka S, Hunjan A, Sharma R, Otsubo H, Chuang S (2005) Volumetric localization of epileptic activities in tuberous sclerosis using synthetic aperture magnetometry. *Pediatr Radiol* 2005 Oct 21 1-6 [Epub ahead of print]

Zhang Y, Billington Jr CJ, Pan D, Neufeld T (2005) Drosophila Target of Rapamycin Kinase Functions as a Multimer. Genetics 2005 Oct 11 [Epub ahead of print]

NEW TSC RESOURCES

TSC1 CONDITIONAL KNOCKOUT MICE AVAILABLE SOON FROM JACKSON LABORATORY Stock #005680 STOCK Tsc1<tm1Djk>/J arrived at the Importation Facility at The Jackson Laboratory. A description of the new strains under development process and associated time requirements are described in "Frequently Asked Questions" at <http://jaxmice.jax.org/support/faq/index.html>

We monitor the interest for strains under development via calls to our Customer Service and Technical Support Representatives registered interest on our web page. If there is sufficient interest in a strain accepted for inclusion in the Cryopreservation Resource, we will establish a distribution colony.

Please encourage investigators who might contact you about obtaining this strain to register their interest on our Strains Under Development web page. This will ensure that they receive advance notification of pending availability.

The URL for the strain Data Sheet with a link to register interest is:
<http://jaxmice.jax.org/micedata.shtml?005680>

Other TSC mouse models:

Tsc1+/- is at the MMHCC resource at NCI: <http://web.ncifcrf.gov/researchresources/mmhcc/default.asp>
Tsc2+/- is at JAX: <http://jaxmice.jax.org/jaxmice-cgi/jaxmicedb.cgi?objtype=pricedetail&stock=004686>

CONFERENCES

December 2-6, 2005

American Epilepsy Society & American Clinical Neurophysiology Society

Washington, DC Convention Center
Washington, DC

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

****Come to the TSC SIG at this year's meeting on Saturday, December 3, 2006, and visit the TS Alliance exhibit!**

January 5-7, 2006

Genetics Society of America meeting: GENETIC ANALYSIS: From Model Organisms to Human Biology

Abstract Deadline: November 14, 2005

Location: San Diego, CA

For more information on the meeting see:

<http://www.gsa-modelorganisms.org/>

January 8 - 13, 2006

Keystone Symposium on Genome Sequence Variation and the Inherited Basis of Common Disease and Complex Traits

Abstract Deadline: October 4, 2005

Early Registration Deadline: November 7, 2005

Location: Big Sky Resort, Montana

For more information and to register, please visit:

<http://www.keystonesymposia.org/Meetings/ViewMeetings.cfm?MeetingID=787&CFID=1196412&CFTOKEN=19360022>

March 31 – April 2, 2006

LAM Foundation 2006 Research Conference

Hilton Netherlands Cincinnati Hotel

Cincinnati, OH

<http://lam.uc.edu>

May 3-5, 2006

TSC International Research Conference 2006

Spandau, Ev. Johannesstift

Hotel "Christophorus Haus"

Berlin, Germany

<http://www.tsc2006.org>

SAVE THE DATE! May 11-12, 2006

Hamartoma Syndromes and Insulin Signaling

Lister Hall, National Institutes of Health, Bethesda, MD

More information coming soon!

July 2-6, 2006

7th European Congress of Epileptology

Helsinki Fair Centre, Helsinki, Finland

<http://www.epilepsyhelsinki2006.org>

July 8-12, 2006

UICC World Cancer Congress 2006

Washington Convention Center, Washington, DC

<http://www.2006conferences.org/u-program.php>

Submit abstracts to UICC 2006 through the official conference website at

http://2006.confex.com/2006/uicc/index_UICC.epl

All abstracts must be submitted electronically.

For more information about abstract submission, please see

<http://www.2006conferences.org/u-abstracts.php>

SAVE THE DATE! July 14-16, 2006

National TSC Conference

Organized by the Tuberous Sclerosis Alliance

[Indian Lakes Resort](http://www.tsalliance.org)

Chicago, Illinois

<http://www.tsalliance.org>

October 30 – November 2, 2006

World Congress on Autism

Cape Town, South Africa

Call for Papers closes 30th September 2005

Early Bird Registration Closes June 30th 2006

Please visit www.autismcongress.com

March 2007

NINDS Epilepsy Conference

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

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

NEWS

DIAZEPAM RECTAL GEL DELIVERY SYSTEM (DIASTAT AcuDial) FOR AT-HOME SEIZURE TREATMENT

On Sept. 15, the FDA approved a new delivery system for diazepam rectal gel (Diastat AcuDial, made by Valeant Pharmaceuticals International) that enables immediate in-home treatment of emergency seizures by a non-medically trained caregiver.

Using the system, pharmacists can dial, set, and lock in specific doses ranging from 5 to 20 mg using one of two configurations: one with a 4.4-cm tip that delivers doses of 5, 7.5, and 10 mg, and the other having a 6.0-cm tip for delivery of 10-, 12.5-, 15-, 17.5-, and 20-mg doses.

No refrigeration or special handling is required, allowing the device to be stored in the home or office, and taken along when traveling.

The approval was based on data from clinical studies showing that use of the system was effective in resolving seizures in 85% of patients; 71% remained seizure-free for 12 hours after diazepam administration.

Home use of the system was also linked to a 67% decrease in emergency-department visits, and 82% of patients treated with the device in clinical trials were assessed by their caregivers as better compared with 33% of placebo-treated patients ($P < .0001$).

Diazepam rectal gel is indicated for the management of selected refractory patients with epilepsy who are on stable anti-epileptic drug regimens and who require intermittent use of diazepam to control bouts of increased seizure activity.

RESEARCH HIGHLIGHTS FROM THE TSCR

<http://cdmrp.army.mil>

Understanding the Causes of TSC-Related Epilepsy

David H. Gutmann, Ph.D., Washington University School of Medicine, St. Louis Missouri
Funded by the Department of Defense Tuberous Sclerosis Complex Research Program

Epilepsy is one of the most devastating complications of tuberous sclerosis complex (TSC). Approximately 80% of children who have TSC develop epileptic seizures, which are often severe and refractory to available treatments. Seizures and other manifestations of TSC have been attributed to malformed areas in the brain, known as cortical tubers, that are believed to arise during embryonic development. Dr. David Gutmann and colleagues of the Washington University School of Medicine have determined new mechanisms by which TSC gene defects in the brain result in seizures. Understanding such cellular and molecular mechanisms of seizures is necessary for developing new tailored therapies.

With funding from a Department of Defense Fiscal Year 2002 Tuberous Sclerosis Complex Research Program Idea Development Award, Dr. Gutmann and colleagues used mouse models in which the *Tsc1* gene was inactivated in the astrocyte class of neuroglial cells to study TSC-related epilepsy. These mice exhibit enhanced astrocyte proliferation, abnormal neuronal organization, and seizures. The investigators found abnormal expression of neuroglial differentiation markers in *Tsc1*-deficient astrocytes. Similar gene expression patterns were observed in cortical tubers and subependymal giant cell astrocytoma tumors from TSC patients, suggesting that both types of lesions arise from similar neuroglial progenitor cells and that *Tsc1* gene inactivation in humans leads to aberrant progenitor cell differentiation. *Tsc1* loss in mouse astrocytes also was associated with increased activity of the Rheb/mammalian target of rapamycin (mTOR)/p70S6 kinase (S6K) pathway, supporting recent evidence that the TSC1/TSC2 protein complex may regulate Rheb and S6K. In addition, they found that an important astrocyte adhesion molecule, adhesion molecule in glia (AMOG), also regulates the mTOR signaling pathway, but independent of TSC.

Gutmann and colleagues examined the molecular mechanisms that might underlie increased neuronal excitability and lead to seizures. They showed that *Tsc1*-deficient astrocytes had decreased expression of two weak inward

rectifier potassium currents and exhibited diminished potassium current in functional assays. These astrocyte potassium current defects were not reversed by rapamycin, an inhibitor of mTOR. Dr. Gutmann and his team believe that the observed abnormalities in astrocyte potassium uptake could potentially lead to excessive synaptic stimulation in neurons, resulting in hyperexcitability and seizures.

Dr. Gutmann's research team has (1) discovered several genetic and cellular abnormalities that result from astrocyte-specific inactivation of Tsc1, (2) demonstrated that there is a role for astrocyte potassium homeostasis in influencing seizures in mouse models of TSC, and (3) developed a novel concept that the astrocyte may be centrally involved in the pathogenesis of neurological complications of TSC, including epilepsy. Based on these findings, innovative therapies for epilepsy could potentially target astrocytes.

Publications:

Ess KC, Uhlmann EJ, Li W, Li H, DeClue JE, Crino PB, and Gutmann DH. 2004. Expression profiling in tuberous sclerosis complex (TSC) knockout mouse astrocytes to characterize human TSC brain pathology. *Glia* 46:28-40.

Uhlmann EJ, Li W, Scheidenhelm D, Gau CL, Tamanoi F, and Gutmann DH. 2004. Loss of tuberous sclerosis complex 1 (Tsc1) expression results in increased Rheb/S6K pathway signaling important for astrocyte cell size regulation. *Glia* 47:180-188.

Ess KC, Kamp KA, Tu BP, and Gutmann DH. 2005. Developmental origin of subependymal giant cell astrocytoma in tuberous sclerosis complex. *Neurology* 64:1446-1449.

Scheidenheim DK, Cresswell J, Haipek CA, Fleming TP, Mercer RW, and Gutmann DH. 2005. Akt-dependent cell size regulation by the adhesion molecule on glia (AMOG) occurs independently of phosphatidylinositol 3-kinase and Rheb signaling. *Molecular and Cellular Biology* 25:3151-3162.

Jansen LA, Uhlmann EJ, Crino PB, Gutmann DH, and Wong M. 2005. Epileptogenesis and reduced inward rectifier potassium current in tuberous sclerosis complex-1 deficient astrocytes. *Epilepsia* (in press).

RESEARCHERS UNCOVER NEW GENES THAT CONTROL LONGEVITY An effort to understand the molecular mechanisms that control aging has led HHMI researcher, Stanley Fields, Ph.D., University of Washington School of Medicine, and his colleagues to identify 10 new genes (one of them is TOR!) that regulate longevity in yeast. The studies also suggest a new model for how aging is slowed when caloric intake is restricted. This research was published in the November 18, 2005, issue of *Science*. For the full story, go to <http://www.hhmi.org/news/fields20051118.html>

LOSS OF FEAR FACTOR MAKES TIMID MOUSE BOLD HHMI investigator, Eric R. Kandel, M.D., from Columbia University College of Physicians and Surgeons and colleagues have identified a fear factor – a protein the brain uses to generate one of the most powerful emotions in humans and animals. The molecule is essential for triggering both the innate fears that animals are born with – such as the shadow of an approaching predator – as well as fears that arise later in life due to individual experiences. Eliminating the gene that encodes this factor makes a fearful mouse courageous. The finding, the researchers say, suggests new approaches for drugs designed to treat conditions such as phobias, post-traumatic stress disorder, and anxiety. This research was published in the November 18, 2005, issue of *Cell*. For the full story, go to <http://www.hhmi.org/news/kandel20051118.html>

DISCOVERY PROVIDES NEW CLUES ABOUT CAUSES OF RETT SYNDROME HHMI researcher, Huda Y. Zoghbi, M.D., Baylor College of Medicine, and collaborators, studying the childhood neurological disorder Rett syndrome have discovered a new clue about how the disorder can cause a devastating range of symptoms. They found that the protein that is altered in patients with the syndrome also plays a critical role in snipping and rearranging messenger RNA molecules. These molecules carry the genetic code for the construction of other proteins that are important for brain function. This research was published in the October 17, 2005, issue of *Proceedings of the National Academy of Sciences*. For the full story, go to <http://www.hhmi.org/news/zoghbi7.html>

TSC INFORMATION

For information about TSC, 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.