



TSC ALERT

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

June 16, 2003

Welcome to the June 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.

Starting with this issue of *TSC Alert*, we will also include information of interest to health care professionals who provide care for individuals with TSC and their families. See the new **Clinical Trials** section.

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

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GRANT ANNOUNCEMENTS:

Grants Awarded for FY2003 Tuberous Sclerosis Complex Research Program (TSCRCP) in the Congressionally Directed Medical Research Program, Department of Defense

Congratulations to the three Center Without Walls researchers who were awarded grant funds through the TSCRCP! They are:

David Gutmann, M.D., Ph.D.
Washington University, St. Louis, MO

\$424,682
Mouse Models of TSC-Related Epilepsy

Elizabeth Petri Henske, M.D.
Fox Chase Cancer Center, Philadelphia, PA
\$398,751
TSC1 and TSC2 Gene Homologs in *Schizosaccharomyces Pombe*

Naoto Ito, Ph.D.
Massachusetts General Hospital, Charlestown, MA
\$420,569
Functions of TSC Genes in the Nervous System of *Drosophila Melanogaster*

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 postdoctoral 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:

GLOBAL HEALTH RESEARCH INITIATIVE PROGRAM FOR NEW FOREIGN INVESTIGATORS (PAR-03-118)

<http://grants.nih.gov/grants/guide/pa-files/PAR-03-118.html>

INNOVATIONS IN BIOMEDICAL COMPUTATIONAL SCIENCE AND TECHNOLOGY: SBIR/STTR INITIATIVE (PAR-03-119)

<http://grants.nih.gov/grants/guide/pa-files/PAR-03-119.html>

THE FETAL BASIS OF ADULT DISEASE: ROLE OF THE ENVIRONMENT (PAR-03-121)

<http://grants.nih.gov/grants/guide/pa-files/PAR-03-121.html>

DRAFT NIH STATEMENT ON SHARING AND DISTRIBUTING MOUSE RESOURCES: PUBLIC COMMENT PERIOD OPEN UNTIL AUGUST 1, 2003 (NOT-OD-03-043)

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-043.html>

CORRECTED DATES: INNOVATIONS IN BIOMEDICAL COMPUTATIONAL SCIENCE AND TECHNOLOGY INITIATIVES (NOT-OD-03-044)

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-044.html>

NEW NINDS EXPLORATORY/DEVELOPMENTAL GRANT (R21) - NOTICE OF INACTIVATION OF OLD PROGRAM (NOT-NS-00-011) (NOT-NS-03-017)

<http://grants.nih.gov/grants/guide/notice-files/NOT-NS-03-017.html>

NCRR HIGH END INSTRUMENTATION PROGRAM (RFA-RR-03-009)

<http://grants.nih.gov/grants/guide/rfa-files/RFA-RR-03-009.html>

The NINDS has posted a summary online for **the Health Disparities in Epilepsy Planning Panel** meeting that was held in November 2002. It is now available online: http://www.ninds.nih.gov/news_and_events/epilepsy_panel_2002.htm

WEB-BASED EXHIBIT ON GENETICS RESEARCH NOW AVAILABLE

An on-line exhibit on genetics research, sponsored by the Office of NIH History, is now available on the World Wide Web at: <http://history.nih.gov/exhibits/genetics> The exhibit answers important questions about genetics research and features cartoons to increase children's interest in genetics. A physical version of the exhibit is also on display at the NIH Clinical Center.

Titled "Revolution in Progress: Human Genetics and Medical Research," the exhibit looks specifically at how this research will help in the prevention and treatment of disease. It also provides information on what DNA, genes, and chromosomes do in our bodies, explains how basic research has led to a better understanding of genetic research, and discusses the scope, purpose, and techniques of the Human Genome Project to map and decode our genes. The

exhibit poses such questions as: How do genes cause disease? Can gene therapy work? How do we manipulate genes and should we?

"Genetics research is producing discoveries that have profound implications for our society," says historian Dr. Victoria Harden, the Director of the Office of NIH History and its Stetten Museum of Medical Research. "This research will affect everyone's life, and we must struggle individually and as a nation with the ethical questions regarding testing, medical insurance and job discrimination, and gene therapy and eugenics. I'm excited that more people, especially teachers and students, will now be able to see this exhibit on the Internet."

The Office of NIH History and the Stetten Museum are components of the Office of Communications and Public Liaison in the NIH Office of the Director. "Revolution in Progress" was produced by the Stetten Museum in collaboration with the National Human Genome Research Institute, the National Heart, Lung, and Blood Institute, the National Cancer Institute, the National Institute of Allergy and Infectious Disease, and the National Institute of General Medical Sciences. The National Institutes of Health is an agency of the U.S. Department of Health and Human Services.

GENETICS HOME REFERENCE: Makes Genes, Chromosomes, DNA Easily Understood

When you hear "gene map," do you think it's a guide to finding the nearest Gap store? Are you the kind of person who thinks that "genetic markers" are sold at office supply stores?

Now, thanks to the National Library of Medicine (NLM) you can find answers to your genetic questions. With the click of a mouse you can go the NLM's newest consumer web site, "Genetics Home Reference," at <<http://ghr.nlm.nih.gov>>. Genetics Home Reference joins Medlineplus.gov (the consumer site for general medical information) and Clinicaltrials.gov (the site that lists clinical research trials) in the lexicon of NLM's consumer medical web sites.

"The American public is increasingly turning to the Web for medical information," said Donald A.B. Lindberg, M.D., director of the National Library of Medicine. "The launch of Genetics Home Reference was a logical step in making genetics and its relationship to disease more understandable to the general public," said Lindberg.

"Knowledge about genetics is vital for a true understanding of many diseases," says Alexa T. McCray, Ph.D., director of NLM's Lister Hill National Center for Biomedical Communications, the organization responsible for creating this innovative website. "Often, individuals need to make life-altering decisions because of their genetic background. We hope that Genetics Home Reference can help guide them as they make their medical choices."

The target audience is the general public, and the language is written at the high school level - for those who remember "a little from their high school biology course." A quick refresher course is available by clicking the "help me understand genetics page" which talks about, for example, how genes can be turned on and off in cells, what it means if a disorder seems to run in a family, and the principles of gene mutation. Explanations are written in simple and understandable English.

If you have questions about a specific disease you browse either by disease/condition or by gene. If you type in Alzheimer's disease, for instance, a page appears where the information is written in a question and answer format. You'll find out how people inherit Alzheimer's, the symptoms, and what treatments are available. There's also a geographic listing of genetic counselors and information for caregivers. In addition, you can easily find details on the specific genes related to Alzheimer's.

Other features are a glossary of genetic terms, links that take you to clinical trials related to the disorder you're searching, and more advanced genetic information. Genetics Home Reference will be adding genetic diseases on a regular basis and the information will be updated as needed.

The National Library of Medicine is a part of the National Institutes of Health, an agency of the U.S. Department of Health and Human Services.

CLINICAL TRIALS:

PEDIATRIC OFF-PATENT DRUG STUDY (PODS) CENTER - LORAZEPAM - STATUS EPILEPTICUS (NOT-HD-03-012)

National Institute of Child Health and Human Development

<http://grants.nih.gov/grants/guide/notice-files/NOT-HD-03-012.html>

Rapamycin Clinical Trial for TSC and LAM Begins in Cincinnati!

July 1, 2003 will mark the first day of the clinical trial for the treatment of kidney and lung manifestations of Tuberous Sclerosis Complex (TSC) and/or Lymphangiomyomatosis (LAM) in Cincinnati, OH. Co-sponsored by the Tuberous Sclerosis Alliance and the LAM Foundation, this clinical trial will enroll adults with TSC and/or LAM who will receive treatment with Rapamycin, and their kidney and lung involvement will be followed over the course of two years.

How does Tuberous Sclerosis Complex affect the kidneys and lungs?

Tuberous sclerosis complex (TSC) is a genetic condition characterized by lesions of the skin and central nervous system, tumor growth, seizures and cognitive and behavioral issues. The birth incidence of this disorder is approximately one in 6,000. In the kidney, TSC can present as five different lesions: benign or malignant renal angiomyolipomas (AMLs), oncocytomas, renal cell carcinoma (RCC) and renal cysts. Of these five types, AMLs are the most common kidney lesion, occurring in 70-80% of adults and children with TSC, and representing the second most common cause of morbidity in TSC. AMLs are lesions comprised of abnormal blood vessels, smooth muscles, and fat cells. Spontaneous bleeding of the abnormal blood vessels, and the compromise of normal kidney function due to enlarged AMLs, account for most of the kidney problems experienced by those with TSC. Individuals with TSC and renal AMLs have a greater risk of developing malignant kidney tumors than do individuals with renal AMLs who do not have TSC. Unfortunately, at the present time, removal of kidney AMLs through embolization or invasive surgery is the only treatment options.

In individuals with TSC, particularly women, AMLs are frequently associated with LAM. LAM is a progressive pulmonary disorder characterized by smooth muscle infiltration and cystic destruction of the lung. LAM is far more common in women with TSC than in men (although cases of men with TSC and LAM have been reported), with the average age of onset occurring between 32-34 years of age. The first sign of lung involvement in an individual with TSC may be shortness of breath after mild exercise, spontaneous lung collapse, or cough. Progression to pulmonary failure may develop, but not usually until the third or fourth decade of life. A recent protocol at the NIH revealed that close to 40% of women with TSC have manifestations of LAM, but the majority of these women do not show any symptoms of LAM. Recent research studies in Elizabeth Petri Henske's laboratory at Fox Chase Cancer Center in Philadelphia have produced evidence that the migration of cells from kidney AMLs to the lungs may be involved in the

development of LAM in individuals with TSC and sporadic LAM. This research highlights the possible relationship between AMLs and LAM, indicating that studies examining ways to reduce the size of AMLs may also produce effective LAM treatment strategies.

Why has rapamycin been selected as a potential treatment strategy for clinical trials?

Both LAM and AML cells contain a functionally inactivating inherited or developmental mutation in either of their tuberous sclerosis genes, TSC1 or TSC2. This produces a deficiency of their protein products hamartin or tuberin, respectively. How deficiencies in tuberin or hamartin caused tumor growth was unclear until recently, when researchers discovered that the TSC proteins play a significant role in the life cycle and proliferation of cells. These research studies have yielded evidence that the TSC proteins are involved in the regulation of a molecular signaling event, called the PI3K/Akt/S6K signaling pathway that controls cellular proliferation. Specifically, tuberin and hamartin associate into a complex that functions to inhibit the actions of the kinase mTOR, or mammalian target of rapamycin. As the name implies, mTOR is also the inhibitory target of rapamycin, a drug currently marketed by Wyeth-Ayerst. Genetic mutations that result in the absence or dysfunction of tuberin or hamartin, as occur in patients with TSC and LAM, causes mTOR to be continually activated, resulting in abnormal cell growth and division. Rapamycin functions exactly like the tuberin/hamartin complex by inhibiting the activity of mTOR. Exciting preliminary data presented at the Tuberous Sclerosis Research Conference in Chantilly, Virginia, has demonstrated that rapamycin causes shrinkage of renal tumors in mouse and rat. These results have identified rapamycin as an extremely promising treatment strategy for kidney tumors.

What are the current applications for rapamycin?

Rapamycin has been commercially available in the US for 2 years for treatment to suppress the immune system to prevent organ rejection following transplantation. It is FDA-approved for this indication in adults and children over 13 years of age. Rapamycin has also been used for the treatment of rejection following islet cell, small bowel, liver, and heart transplantation, as well as preservation of coronary artery stents. Common side effects include anemia, thrombocytopenia, and hypercholesterolemia.

What is the purpose of the rapamycin clinical trial?

In TSC, mutations in the TSC genes causes abnormal signaling within cells, resulting in cellular overgrowth and abnormal proliferation. The aim of the rapamycin clinical trials is to restore the signaling balance of these pathways through the administration of rapamycin. With the signaling pathways properly balanced, it is hoped that AMLs can be inhibited from growing and possibly even regress. Given the likely relationship between AMLs and LAM, rapamycin may also affect the growth of pulmonary tumors as well.

Who will participate in this trial and how will it be conducted?

Thirty participants, age 18 to 65, male and female, will be selected from individuals followed at the Tuberous Sclerosis Clinic at Children's Hospital Medical Center in Cincinnati. Individuals with sporadic LAM (in which there is not a clinical TSC diagnosis) will be selected as well. Entering participants will undergo a history and physical examination by one of the investigators. Also included in the baseline evaluation will be kidney MRI scans (including MR spectroscopy), baseline laboratory studies including renal profiles, liver profiles, and fasting lipid profiles. Blood will be drawn for genomic analysis to determine the presence of TSC mutations. In addition, individuals with evidence of LAM will have baseline pulmonary function tests consisting of spirometry and lung volumes. After initiation of rapamycin, follow-up evaluations will be performed at two weeks, one month, two months, four months, six months, and twelve months, eighteen months, and twenty-four months. Laboratory studies and rapamycin levels will be obtained at each follow-up visit; in addition, kidney MRI scans and a chest CT scan (for those

participants with LAM) will be performed. Participants with TSC will also be observed for rapamycin's effect on cortical tumors and subependymal nodules in the brain.

What is the measure of success for this trial?

Participants will be considered to have a response to rapamycin treatment if their AML size decreases by thirty percent or more from baseline. Participants will be considered to have a complete response to rapamycin treatment if their AML size decreases by seventy-five percent or more.

What are the plans for future clinical trials?

Clinicians and researchers are currently considering a multi-center clinical trial of rapamycin that would include hundreds of individuals with TSC and LAM throughout the USA and UK. In addition, researchers are examining the possibility of using other drugs that are similar to rapamycin (called drug analogues) with fewer side effects and/or other medications. In addition, research utilizing model systems of TSC will continue to explore the role of varying dosages and treatment protocols for rapamycin, as well as other treatments.

NEW TSC PUBLICATIONS:

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Elhence V, Mehta B, Jain M, Gupta RK (2002) Renal angiomyolipoma: a clinico-pathological study or eleven cases. *Indian J Cancer* 39(2):55-60

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- Krymskaya VP (2003) Tumour suppressors hamartin and tuberlin: intracellular signalling. *Cell Signal* 15(8):729-39
- Li S, Braverman R, Li H, Vass WC, Lowy DR, DeClue JE (2003) Regulation of cell morphology and adhesion by the tuberous sclerosis complex (TSC1/2) gene products in human kidney epithelial cells through increased E-cadherin/beta-catenin activity. *Mol Carcinog* 37(2):98-109
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22(12):3073-83

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Saucedo LJ, Gao X, Chiarelli DA, Li L, Pan D, Edgar BA (2003) Rheb promotes cell growth as a component of the insulin/TOR signalling network. *Nat Cell Biol* 5(6):566-71

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Yeniyol CO, Zeyrek N, Parildar M, Selek E, Tasli F, Memis A (2002) Life threatening hematuria in a patient with renal angiomyolipoma and selective renal embolization prior to nephrectomy. *Int Urol Nephrol* 34(2):185-8

Zhang Y, Gao X, Saucedo LJ, Ru B, Edgar BA, Pan D (2003) Rheb is a direct target of the tuberous sclerosis tumour suppressor proteins. *Nat Cell Biol* 5(6):578-581

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:

- Tuber
- SEGA

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>

CONFERENCES:

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

Oct 1 - 4, 2003

2003 Child Neurology Society Annual Meeting

Loew's Hotel, Miami Beach, FL

Online registration coming in June at: http://www.childneurologysociety.org/events/evt_001.asp

October 1, 2003

7:30 am –5:00 pm

SATELLITE SYMPOSIUM to CNS Annual Meeting

Tuberous Sclerosis Complex

CME ACTIVITY

Moderator: Bernard L. Maria, MD, MBA, Children's Miracle Network Distinguished Professor of Child Health, University of Missouri School of Medicine, Columbia, MO

7:30 AM - 7:45 AM

Introduction and Statement of Symposium Goals

Bernard L. Maria, MD, MBA

CURRENT APPROACHES TO DIAGNOSIS OF TUBEROUS SCLEROSIS

Moderator: Steve Roach, MD

Wake Forest University Baptist Medical Center, Winston-Salem, NC

7:45 AM – 8:15 AM

Overview and approaches to diagnosis

Steve Roach, MD

8:15 AM – 8:45 AM

Brain abnormalities in TS

Francis DiMario, MD

University of Connecticut Health Center, Hartford, CT

8:45 AM – 9:15 AM

Imaging of TS

Edward Bullmore, MD

University of Cambridge, Cambridge, United Kingdom

9:15 AM – 9:45 AM

Behavior aspects of TS

Penny Prather, PhD

Harvard Medical School, Boston, MA

9:45 AM – 10:15 AM

Autism in TS

Max Wiznitzer, MD

Case Western Reserve University, Cleveland, OH

10:15 AM – 10:30 AM

Additional Question and Answer Session

10:30 AM – 11:00 AM

BREAK

TREATMENT AND MANAGEMENT OF COMPLICATIONS

Moderator: Steve Roach, MD

11:00 AM – 11:30 AM

Managing epilepsy in TS

Elizabeth Thiele, MD, PhD

Harvard Medical School, Boston, MA

11:30 AM – 11:50 AM

Surgical treatment of TS

Howard Weiner, MD

New York University School of Medicine, New York, NY

11:50 AM – 12:10 PM

Non-neurologic complications of TS

David Franz, MD

Cincinnati Children's Hospital Medical Center, Cincinnati, OH

12:10 AM – 12:30 PM

Additional Question and Answer Session

12:30 PM – 1:30 PM

LUNCH

GENETIC STRATEGIES IN TUBEROUS SCLEROSIS

Moderator: David Gutmann, MD, Donald O. Schnuck Family Chair and Professor of Neurology,
Washington University School of Medicine, St. Louis, MO

1:30 PM – 1:50 PM

Clinical genetics of TS

Hope Northrup, MD

The University of Texas Medical School at Houston, Houston, Texas

1:50 PM – 2:10 PM

Molecular genetics of TS

Elizabeth Henske, MD

Fox Chase Medical Center, Philadelphia, PA

2:10 PM – 2:40 PM

TS genes and the brain

Peter Crino, MD, PhD
University of Pennsylvania Health System, Philadelphia, PA

2:40 PM – 3:10 PM

[Mouse models of TS](#)
David Gutmann, MD

3:10 PM – 3:30 PM

[Additional Question and Answer Session](#)

3:30 PM – 4:00 PM

BREAK

FUTURE DIRECTIONS AND INNOVATIVE THERAPIES

4:00 PM – 4:45 PM

Moderators: Robert Finkelstein, PhD, Program Director, Neurogenetics Cluster, NINDS, and Vicky Whittemore, PhD, Tuberous Sclerosis Alliance, Silver Spring, MD

4:45 PM – 5:00 PM

[Closing Comments](#)
Bernard L. Maria, MD, MBA

Supported by grants from the National Institutes of Health (NIH grant 1 R13 NS40925-01), the Tuberous Sclerosis Alliance, and the Child Neurology Society

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