



TSC ALERT

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Welcome to the December 2003 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 January 2004 *TSC Alert* contact: Vicky.Whittemore@tsalliance.org



**Happy Holidays from
the TS Alliance!**



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GRANT ANNOUNCEMENTS:

SUMMER RESEARCH FUNDING ANNOUNCED

The Marine Biological Laboratory in Woods Hole, Massachusetts has announced the availability of funding for two summer research programs in neuroscience in 2004; the Albert and Ellen Grass Faculty Grants Program, and the Dart Foundation Scholars Program in Learning & Memory. These programs will provide up to \$50,000/year/award with a possibility for renewal for 3 years. The application deadline is Friday, January 30, 2004. For more information visit the Web site <http://www.mbl.edu/research/summer/fellowships.html> or e-mail Sandra Kaufmann at skaufmann@mbl.edu

NEW DEADLINES FOR MINORITY NEUROSCIENCE FELLOWSHIP POSTDOCTORAL APPLICANTS

To offer more flexibility to postdoctoral candidates, the Minority Neuroscience Fellowship Program through the Society for Neuroscience now offers three deadlines (Jan. 1, April 1, and Sept. 1). The program is designed to increase diversity in neuroscience with a special focus on increasing numbers of traditionally underrepresented racial and ethnic minorities engaged in research in preeminent laboratories. For more information please visit <http://www.sfn.org/mnfp>.

NIH ANNOUNCEMENTS:

TAKE A SURVEY FOR NHGRI

In the summer of 2002 the National Human Genome Research Institute (NHGRI) launched a re-design of its website (www.genome.gov). Now that the site has been active for over a year, NHGRI is evaluating its effectiveness. As part of this evaluation, NHGRI has posted a survey on [genome.gov](http://www.genome.gov) to let visitors to tell the Institute what they think is working, what is not working, and how the site can be improved. Once the evaluation is complete, this information will be used to tailor the design and content of the site to better serve visitors.

If you use [genome.gov](http://www.genome.gov), even infrequently, please help NHGRI by taking its short (5 minute) survey the next time you visit the site at <http://www.genome.gov>

NEW GRANTS.GOV WEB SITE OFFERS ONE-STOP SHOPPING FOR INFORMATION ON APPLYING FOR ALL FEDERAL GRANTS

Site Supports President's E-Gov Initiative By Improving Grant Application Process

HHS Secretary Tommy G. Thompson today unveiled a single, comprehensive Web site that will contain information about finding and applying for all federal grant programs. The Web site, [Grants.gov](http://www.grants.gov), makes it easier for organizations to learn about and apply for federal grants. Its launch marks an important milestone in President Bush's Electronic Government (E-Gov) Initiative. HHS led the development of the cross-agency Web site, which now has information about more than 800 available grant programs involving all 26 federal grant-making agencies. These agencies together award more than \$360 billion in grant funds. The site provides information in a standardized format across agencies and includes a "Find Grant Opportunities" feature to help applicants find potential funding opportunities.

The site also contains an "Apply for Grants" feature that greatly simplifies the application process by allowing applicants to download, complete and submit applications for specific grant opportunities from any federal grant-making agency.

To date, application packages have been posted to the Grants.gov Web site by five agencies -- the U.S. Departments of Commerce, Education, Energy, Justice and HHS. This section will be expanded in the coming months as federal agencies continue to post application information about additional grant opportunities.

Grants.gov is a collaborative effort involving HHS and the Departments of Agriculture, Commerce, Defense, Education, Homeland Security, Housing and Urban Development, Justice, Labor and Transportation, as well as the National Science Foundation.

More information about Grants.gov is available at <http://www.grants.gov> More information about the President's E-Gov Initiative is available at <http://www.whitehouse.gov/omb/egov>

CLINICAL STUDIES OF SAFETY AND EFFECTIVENESS OF ORPHAN PRODUCTS: AVAILABILITY OF GRANTS

The Food and Drug Administration (FDA) is announcing changes to its Office of Orphan Products Development (OPD) grant program for fiscal years (FY) 2004 and 2005. This announcement supercedes the previous announcement of this program, which was published in the Federal Register of August 27, 2002 (67 FR 55020). For FY 2004, the application receipt date is October 13, 2003. For FY 2005, the application receipt dates are April 7, 2004, and October 6, 2004.

<http://www.fda.gov/orphan/grants/2004RFA.htm>

STATEMENT BY THOMMY G. THOMPSON, Secretary of Health and Human Services On the Signing of the Pediatric Research Equity Act of 2003

President Bush today signed important new legislation that will improve the quality of health care for our children. The Pediatric Research Equity Act of 2003 gives the Food and Drug Administration clear authority to require pediatric studies of drugs when needed to ensure that they are safe and effective for children.

Children need access to effective drugs to treat their ailments, and those drugs should be properly tested for pediatric use rather than just prescribed and sold based on adult testing. This legislation will allow the FDA to require such studies when appropriate and will better assure doctors and parents alike that the drugs used to treat our children are safe and will work as expected.

The administration has worked diligently with Congress to enact this legislation quickly, in order to make FDA's authority clear. I thank all the members who worked hard to make this happen for our nation's children.

REVISED RFA DESIGNATORS FOR NIH ROADMAP INITIATIVES (NOT-OD-04-008)

National Institutes of Health

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-008.html>

INTERDISCIPLINARY HEALTH RESEARCH TRAINING: BEHAVIOR, ENVIRONMENT AND BIOLOGY

A new [NIH Roadmap Initiative](#), (RFA-RM-04-010), will support the establishment of postdoctoral training programs that provide research training and formal coursework in a new interdisciplinary field to individuals holding advanced degrees in different disciplines. These training programs must include a behavioral or social science discipline. The NIH is especially interested in programs integrating behavioral and/or social sciences with more traditional biomedical sciences (e.g. neuroscience, genetics, molecular biology, cell biology, physiology, etc.).

Letter of Intent Receipt Date: February 11, 2004

Application Receipt Date: March 11, 2004

<http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-04-010.html>

DYNAMIC ASSESSMENT OF PATIENT-REPORTED CHRONIC DISEASE OUTCOMES

(RFA-RM-04-011)

Letter of Intent Receipt Date: February 22, 2004

Application Receipt Date: March 22, 2004

<http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-04-011.html>

ORAL HEALTH OF SPECIAL NEEDS AND OLDER POPULATIONS (PA-04-031)

National Institute of Dental and Craniofacial Research

National Institute on Aging

<http://grants.nih.gov/grants/guide/pa-files/PA-04-031.html>

RUTH L. KIRSCHSTEIN NATIONAL RESEARCH SERVICE AWARDS FOR INDIVIDUAL PREDOCTORAL FELLOWS (F31) (PA-04-032)

National Institute on Alcohol Abuse and Alcoholism

National Institute of Biomedical Imaging and Bioengineering

National Institute on Deafness and Other Communication Disorders

National Institute on Drug Abuse

National Institute of Mental Health

National Institute of Neurological Disorders and Stroke

<http://grants.nih.gov/grants/guide/pa-files/PA-04-032.html>

CIRCULATING CELLS IN CANCER DETECTION (PA-04-035)

National Cancer Institute

<http://grants.nih.gov/grants/guide/pa-files/PA-04-035.html>

CHANGE TO PAR-03-007 - NOVEL GENETIC METHODS TO MAP FUNCTIONAL NEURONAL CIRCUITS AND SYNAPTIC CHANGE (NOT-DA-04-003)

National Institute on Drug Abuse

<http://grants.nih.gov/grants/guide/notice-files/NOT-DA-04-003.html>

CORRECTION TO RFA-DK-03-024: PROTEOMICS AND METABOLOMICS IN TYPE 1 DIABETES AND ITS COMPLICATIONS (NOT-DK-04-001)

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Allergy and Infectious Diseases

National Eye Institute

National Heart, Lung, and Blood Institute

National Institute of Neurological Disorders and Stroke
National Institute of Child Health and Human Development
<http://grants.nih.gov/grants/guide/notice-files/NOT-DK-04-001.html>

NATIONAL ADVISORY MENTAL HEALTH COUNCIL WORKGROUP: SETTING PRIORITIES FOR THE BASIC SCIENCES OF MENTAL HEALTH

<http://www.nimh.nih.gov/council/bsworkshop.cfm>

NHGRI LAUNCHES SOCIAL AND BEHAVIORAL RESEARCH BRANCH: Division of Intramural Research Attracts Duke Researcher to Spearhead Trans-NIH Center on Social and Behavioral Research

The National Human Genome Research Institute (NHGRI) announced today the formation of a new branch -- the Social and Behavioral Research Branch (SBRB) -- within its Division of Intramural Research (DIR). The new branch will develop cutting-edge approaches to translating the discoveries from the recently completed Human Genome Project into interventions for health promotion and disease prevention, and for counseling patients and families dealing with the impact of devastating genetic disorders. The SBRB also will investigate the complex social, ethical and public policy impact of genomic research.

To head the new DIR branch, NHGRI recruited a prominent behavioral epidemiologist from Duke University, Colleen McBride, Ph.D. As director of the Cancer Prevention, Detection and Control Research Program at Duke, Dr. McBride's work focused on developing and evaluating population-based interventions directed at smoking cessation and identifying "teachable moments" for changing behaviors that put people at increased risk for developing disease. Dr. McBride joined the Duke program in 1995 and began serving as the director in 1997.

According to Dr. McBride, the SBRB's research portfolio will encompass four conceptual domains:

- Testing communications strategies aimed at relaying an individual's risk for developing a genetic condition.
- Developing and evaluating interventions aimed at reducing genetically susceptible individuals' risk of acquiring a disease.
- Translating genomic discoveries to clinical practice.
- Understanding the social, ethical and policy implications of genomic research.

There will be a number of research groups within the SBRB. They include a behavioral genetics unit; a health communications unit; a genetic counseling service unit; a health promotion research section that includes a unit for disseminating counseling research methods; a community genetics research unit; and an ethics and social policy unit that includes research ethics. In addition, there will be several cross-cutting themes addressed by researchers in the new branch, including the implications of genomic discoveries and research for health disparities, the ethical and legal implications, and strategies for information dissemination to medical and other communities.

In addition to heading the new NHGRI branch, Dr. McBride also will spearhead the development of a trans-institute Social & Behavioral Science Center (SBSC) within the National Institutes of Health (NIH). The SBSC will be designed to hasten the progress of behavioral and social science research among participating NIH intramural research programs. A cadre of social and behavioral scientists from various NIH institutes and disciplines - including experimental and clinical psychologists, sociologists, geneticists, public health experts, ethicists, decision scientists, community health professionals, informaticists and health communications specialists -- will be

housed together in the new center. Although many NIH institutes sponsor social and behavioral research through their external, or extramural, grants-making divisions, the SBSC will bring a new focus to this type of research among the intramural research community.

The trans-NIH SBSC will house the complete staff of NHGRI's new SBRB as well as investigators and staff from the National Institute of Mental Health (NIMH) and the Office of Behavioral and Social Sciences Research (OBSSR). And because the SBSC is designed to be truly collaborative, faculty and staff from the participating institutes will be intermixed, with offices configured to maximize cross-institute interactions.

The SBSC will achieve several important objectives for all of NIH's intramural research programs. First, it will enable NIH to rapidly respond to evolving research priorities because their proximity can facilitate collaborations among groups of social and behavioral researchers with multidisciplinary perspectives. Second, it will create economies of scale by providing access to a shared infrastructure, including sophisticated cognitive and behavioral assessment technologies, statistical expertise, visiting scholars and trainees, and common library and meeting space. Third, it gives an identity and high visibility to social and behavioral research within the NIH intramural research program. And finally, it allows for interdisciplinary and cross-institute training and career development for intramural scientists who want to gain or sharpen their expertise in social and behavioral research.

To access information about NHGRI's new SBRB, go to <http://www.genome.gov/11508936>.

CHIMP GENOME ASSEMBLED BY SEQUENCING CENTERS: Draft Sequence Aligned With Human Genome

NHGRI announced the first draft version of the genome sequence of the chimpanzee and its alignment with the human genome. All of the data have been deposited into free public databases and are now available for use by scientists around the world. The sequence of the chimpanzee, "Pan troglodytes", was assembled by NHGRI-funded teams led by Eric Lander, Ph.D., at The Eli & Edythe L. Broad Institute of the Massachusetts Institute of Technology and Harvard University, Cambridge, Mass.; and Richard K. Wilson, Ph.D., at the Genome Sequencing Center, Washington University School of Medicine, Saint Louis.

Researchers deposited the initial assembly, which is based on four-fold sequence coverage of the chimp genome, into the NIH-run, public database, GenBank, <http://www.ncbi.nih.gov/Genbank>. In turn, Genbank will distribute the sequence data to the European Molecular Biology Laboratory's Nucleotide Sequence Database, EMBL-Bank <http://www.ebi.ac.uk/embl/index.html> and the DNA Data Bank of Japan, DDBJ <http://www.ddbj.nig.ac.jp>

To facilitate biomedical studies comparing regions of the chimp genome with similar regions of the human genome, the researchers also have aligned the draft version of the chimp sequence with the human sequence. Those alignments can be scanned using the University of California, Santa Cruz's Genome Browser, (<http://genome.ucsc.edu/cgi-bin/hgGateway>) the National Center for Biotechnology Information's Map Viewer, <http://www.ncbi.nlm.nih.gov/mapview> and the European Bioinformatics Institute's Ensembl system <http://www.ensembl.org/>

For more on the scientific rationale for sequencing the chimp genome, go to: <http://www.genome.gov/Pages/Research/Sequencing/SeqProposals/ChimpGenome2.pdf>

For more on comparative genomic analysis, go to: <http://www.genome.gov/10005835>

TSC TISSUE AVAILABILITY:

The Brain and Tissue Banks at Baltimore and at the University of Miami are established to advance the research of [*developmental disorders*](#). The objective of this human tissue repository is to systematically collect, store, and distribute [*brain and other tissues*](#) for research dedicated to the improved understanding, care and treatment of individuals with developmental disorders. The Brain and Tissue Bank for Developmental Disorders at the University of Maryland, Baltimore, works closely with the TS Alliance to coordinate tissue donations from individuals with TSC at the time of surgery or autopsy. If you would like to receive tissue from the tissue, please complete the Tissue Transfer Form, obtained on their website at: <http://som1.umaryland.edu/braintissuebank/>

RESOURCES:

SIGNAL TRANSDUCTION KNOWLEDGE ENVIRONMENT

Check out the resources and links on this Web site focused on signal transduction sponsored by *Science*. <http://www.stke.org>

THE WORLD OF DNA

Hosted by the Cold Spring Harbor Laboratory in New York, DNA Interactive is a primer on the structure, function, and uses of DNA designed for high school and lower-level college students, or for those who need some basic information about genetics. The site utilizes graphics to draw the viewer in and to help explain concepts. Visit the site at: <http://www.dnai.org>

A MAP OF HUMAN VARIATION

The HapMap Project, a project to map how humankind varies genetically, has unveiled its web site, along with the first batch of data. The HapMap Project is making a “haplotype map” of common patterns of variation by examining mutations in the DNA of 270 people of European, Nigerian, Japanese, and Chinese descent. The public data should be a boon to researchers looking for genes that make people susceptible to disease or side effects from drugs.

A year into the 3-year project, the HapMap Project released over 13 million genotypes from 145,554 mutations, known as SNPs. You can browse alleles for mutation frequencies, or get genotype data for individuals by registering and agreeing to conditions, such as not patenting the data. Visit the site at: <http://www.hapmap.org>

NEWS:

TUBEROUS SCLEROSIS ALLIANCE HOLDS SCIENTIFIC ADVISORY PANEL DISCUSSION

The first TSC Scientific Advisory Panel Roundtable Discussion took place on Sunday November 9, 2003 in New Orleans, LA in conjunction with the 33rd Annual Meeting of the Society for Neuroscience.

The Tuberous Sclerosis Alliance (TS Alliance) supports the advancement of tuberous sclerosis complex (TSC) research by providing grants, resources and mechanisms for expanding

awareness of TSC in the clinical and basic science research communities. The TS Alliance is proud of their latest effort to increase TSC awareness, through the inception of the TS Alliance Scientific Advisory Panel Roundtable Discussion.

Panelists participating in Roundtable Discussions were Zach Hall, Ph.D., University of Southern California; Gregory Holmes, M.D., Dartmouth Hitchcock Medical Center; Joel Moss, M.D., Ph.D., Pulmonary Critical Care Medicine NHLBI, NIH; and Cheryl Walker, Ph.D. Univ. Texas M.D. Anderson Cancer Center. By joining with the TSC research community, the Scientific Advisory Panel will assist the TS Alliance in defining its role in both current and future TSC scientific endeavors. Future Roundtable Discussion participants and topics will reflect recent advancements in TSC research. Story Landis, Ph.D. (Director, NINDS, NIH) and Robert Finkelstein, Ph.D. (Program Director, NINDS, NIH) also attended the meeting and provided thoughtful suggestions and comments on the future directions of TSC research.

The main topic of discussion for the Panel was "Do the TSC1 and TSC2 Genes Have a Unique Function in the Central Nervous System?" This topic was selected so that a discussion of our current knowledge of the function of the genes in other organ systems can be discussed in comparison to what we know about the function of the genes in the central nervous system (CNS). This information was provided in short talks by TSC researchers. **D.J. Pan, Ph.D. (UT Southwestern)** discussed the use of *Drosophila* as a model to examine the function of the TSC gene products. **David Kwiatkowski, M.D., Ph.D. (Brigham & Women's Hospital)** summarized the genotypes and phenotypes of current animal models being used to study TSC. **Elizabeth Petri Henske, M.D. (Fox Chase Cancer Center)** discussed the pathogenesis of LAM and renal angiomyolipomas (AMLs), including the benign metastasis or cells their recent finding of multiple vessel types within renal AMLs. Finally, Dr. Henske described the use of the yeast model, *S. pombe*, as a new TSC model system. **Tom Darling, M.D., Ph.D. (USUHSC)** described the cellular composition of TSC skin lesions, and the use of human TSC skin tissue in genetic and biochemical studies. **Vicky Whittemore, Ph.D. (TS Alliance, substituting for David Franz, M.D., Children's Hospital Medical Center)** reviewed the recent results from the clinical study currently underway in Cincinnati that examines the effect of rapamycin on the size of AMLs in both TSC and sporadic LAM individuals. **Vijaya Ramesh, Ph.D. (Massachusetts General Hospital)** discussed the function of hamartin and tuberlin in the CNS and their recent data on Pam (Protein associated with Myc), which is expressed only in brain and contains a zinc finger domain which interacts with tuberlin. **Scott Baraban, Ph.D. (UCSF)** discussed recent studies examining epilepsy in TSC. Although 80-90% of all TSC patients develop epilepsy, little is known about the electrophysiology of seizures in individuals with TSC. Dr. Baraban has also described the electrophysiology of CNS tissue from one individual with TSC who had intractable seizures and underwent surgery to remove the epileptic focus. **Bernardo Sabatini, M.D., Ph.D. (Harvard)** discussed cell-autonomous signaling and the TSC pathway, looking specifically at changes in the dendritic spines of neurons from TSC1 conditional mice. **Elizabeth Thiele, M.D., Ph.D. (Massachusetts General Hospital)** provided an excellent overview of the presentations, as well as a summary of the areas of translational research currently relevant to research on TSC. Dr. Thiele emphasized the involvement of the CNS as a hallmark of TSC, and suggested that individuals with TSC may provide an excellent avenue for studying autism and tumor biology.

ROUNDTABLE SESSION The afternoon roundtable session focused on identifying immediate and long term future research directions for both basic and clinical TSC science. It was unanimously agreed that an annual open TSC conference bringing both clinical and basic TSC professionals together would greatly help to facilitate TSC research. The following action items were also identified:

Basic Research:

1. Regulation of mTOR by Rheb:
 - a. Is this the only TSC2 effector in this pathway?
 - b. How does mTOR sense amino acid levels?
2. Role of the TSC genes in development- examination of neural crest origins.
3. LOH and loss of function studies, particularly in:
 - a. Kidney/AML/LAM
 - b. Rhabdomyomas
 - c. Angiofibroma
4. Examination of haploinsufficiency and identification of modifier genes in TSC- PTEN identified as a solid second hit candidate. Other non-TSC related candidates, that increase TSC symptoms, include:
 - a. Surfactin-B
 - b. Serotonin
 - c. Glutamate
5. Migration studies including:
 - a. GTP rho-mediated.
 - b. Examination of wound healing in TSC mice.
 - c. Melanocyte migration defect
 - i. Is it impacting brain development?
 - d. Examination of apparent migration in human CNS- unusual lines found in the white matter of some TSC individuals.
6. Phosphatase regulation of TSC signaling, including the study of PP6 as a possible mTOR phosphatase.
7. Development/etiology of both LAM and TSC including the study of:
 - a. LAM
 - i. Pluripotent stem cell
 - ii. Mesenchymal/epithelial
 - b. CNS Tubers
 - i. Neuronal progenitors
8. Hamartin:Tuberin interactions
 - a. TSC1 does not equal TSC2
 - i. Disease severity varies in mice and men.
 - ii. Other functions of TSC1?
 - b. Effect of phospho-tuberin is controversial.
 - i. Insulin treatment does (in flies), and does not (in mice) disrupt TSC1/TSC2 complex.
9. Search for new therapeutic targets
 - a. Farnesyl transferase inhibitors
 - b. Inhibitors of Hif/2alpha
 - c. Inhibitors of S6K
 - d. Inhibitors of INFg/STAT3

Clinical Research:

1. Generation of a natural history database.
2. Rapamycin clinical trial – Based on the research, it was agreed that the trial was warranted. However, research questions still need to be addressed, including:
 - a. Rapamycin crossing the blood brain barrier, and its effect in the CNS.
 - b. Timing of treatment.
 - c. Average growth rate of AMLs

3. Development of better detection methods for TSC including, the use of blood, urine, and ascites for the detection of TSC mutation.
4. The study of epileptogenesis and TSC
 - a. Part of natural history study
 - b. Increase number of sites that perform electrophysiology on epileptic human tissue from TSC patients

Preclinical Research:

1. Rats/mice
 - a. Use to determine if rapamycin crosses the blood brain barrier.
 - b. Use to determine timing of treatment.
 - i. Treat earlier
2. Need for better animal models
 - a. Modifier genes
 - i. Eker on different genetic background
 - ii. Fisher vs. Long Evans
 - b. Nestin-Cre mouse offers promise because less leaky.

All researchers are urged to provide comments to the TS Alliance as the organization moves forward to draft a comprehensive TSC Research Plan. Watch the TS Alliance Web site for additional information at <http://www.tsalliance.org>

NEW UNDERSTANDING OF INSULIN'S COMPLEXITIES NEEDED TO CONQUER DIABETES

Major advances in signal-transduction research have contributed greatly to understanding the complexities of insulin action, which, when disrupted, can lead to diabetes and other health problems. According to one Howard Hughes Medical Institute investigator, however, further progress is needed to integrate our expanding knowledge with human physiology if the diabetes epidemic that is escalating throughout the world is to be conquered. Research by Morris F. White, Ph.D., Joslin Diabetes Center was published in the December 5, 2003, issue of Science. For the full story, go to <http://www.hhmi.org/news/mwhite3.html>

SUBMIT PROPOSALS FOR NEUROSCIENCE 2004 SYMPOSIA AND MINI-SYMPOSIA

Symposium proposals for the Annual Society for Neuroscience meeting, Neuroscience 2004 (in San Diego, CA, Oct. 23-27, 2004) should be submitted online at <http://www.sfn.org/sympro>.

Also, a new category, Mini-Symposia, has been added to the program for Neuroscience 2004. This new presentation format calls for six speakers and is geared to junior investigators. Guidelines and other details for the submission of Mini-Symposia are available at <http://www.sfn.org/minisympro>. All proposals must be submitted online by Friday, January 9, 2004.

CLINICAL TRIALS/STUDIES:

HEALTH-RELATED QUALITY OF LIFE RISK FACTORS IN CHILDHOOD EPILEPSY: A MULTI-CENTER STUDY

There is an important lack of knowledge about the underlying factors responsible for the poor psychosocial outcome in a significant proportion of people with childhood onset epilepsy. For this reason we wish to invite pediatric epilepsy specialists from across North America to participate in this unique collaborative project to identify the underlying protective and risk factors for health-related quality of life (HRQL) and study the natural history and adaptation of HRQL in children with epilepsy. With these results in hand it will be possible to develop interventions to maximize the HRQL, address the children's relevant and practical day-to-day needs, and improve the psychosocial outcome in this large population.

We propose to develop a large multi-site study of children with epilepsy and explore, simultaneously and longitudinally, a number of selected child, parent, family and environmental factors that may contribute to HRQL in children with epilepsy. The developmental phase of this project, supported by a grant from the CNF/CNS, is intended to test/confirm the feasibility of conducting this study, and to work out the different procedures. We expect that by the end of this process, after one to two years, an R01 proposal will be submitted to NIH for larger funding.

This may be the first collaborative North American project in childhood epilepsy involving many centers to study close to 3000 children with epilepsy. We believe that together we should be able to duplicate the success of oncologists in improving the quality of life of their patients.

You can contact Gabriel Ronen by email 'roneng@mcmaster.ca' for more information and about a collaborator's meeting at the AES meeting in Boston.

Study Collaborators: Gabriel Ronen, David Streiner, Peter Rosenbaum, Michael Boyl, Charles Cunningham, Lucy Lach, Joan Austin

TS ALLIANCE AND LAM FOUNDTION: RAPAMYCIN CLINICAL TRIAL FOR RENAL AND LUNG INVOLVEMENT IN TSC AND LAM

Patients with TSC and/or LAM are being enrolled in a clinical trial to study the effect of rapamycin on tumor growth in these two diseases. **Contact:** Dr. Frank McCormack at frank.mccormack@uc.edu; or 513-558-4831, Dr. John Bissler at john.bissler@chmcc.org, or Dr. David Franz at david.franz@chmcc.org.

NHLBI: LYMPHANGIOLEIOMYOMATOSIS (LAM) PROTOCOL

The Tuberous Sclerosis Alliance encourages women with TSC and physicians who have patients with TSC, whether or not they have been diagnosed with LAM, to participate in this worthwhile study. Studies such as this are the first step in understanding this devastating disease and we are fortunate that the NHLBI has initiated a protocol aimed at understanding the pathogenesis of LAM. If you are interested in further information or have any questions, you may contact NHLBI at 1-877-NIH-LUNG (1-877-644-5864). Choose # 3 from the menu items after dialing. This is a toll free number.

NEW TSC PUBLICATIONS:

New TSC Book: *Tuberous Sclerosis Complex: From Basic Science to Clinical Phenotypes*, Paolo Curatolo, Editor, London: Mac Keith Press together with Cambridge University Press, 2003.

Summary: 'This is clearly the most authoritative and contemporary statement of current knowledge yet published.' from the Foreword by Harvey B. Sarnat. This book correlates new genetic data and basic science, covers clinical presentation, reviews the historical background and current diagnostic criteria, and deals with the recent advances in neuropathology, molecular genetics and neurobiology which give a better understanding of the pathogenesis of the disease. Pediatricians and child neurologists will find this book uniquely useful, as will other health care professionals and researchers with an interest in TSC. This book may be purchased from Cambridge University Press at:

<http://titles.cambridge.org/catalogue.asp?isbn=1898683395>

Research Highlight: Inoki K, Zhu T, Guan KL (2003) **TSC2 Mediates Cellular Energy Response to Control Cell Growth and Survival.** *Cell* 115(5):577-90

Abstract: Mutations in either the TSC1 or TSC2 tumor suppressor gene are responsible for Tuberous Sclerosis Complex. The gene products of TSC1 and TSC2 form a functional complex and inhibit the phosphorylation of S6K and 4EBP1, two key regulators of translation. In a study carried out at the Life Sciences Institute at the University of Michigan, Inoki and collaborators describe that TSC2 is regulated by cellular energy levels and plays an essential role in the cellular energy response pathway. Under energy starvation conditions, the AMP-activated protein kinase (AMPK) phosphorylates TSC2 and enhances its activity. Phosphorylation of TSC2 by AMPK is required for translation regulation and cell size control in response to energy deprivation. Furthermore, TSC2 and its phosphorylation by AMPK protect cells from energy deprivation-induced apoptosis. These observations demonstrate a model where TSC2 functions as a key player in regulation of the common mTOR pathway of protein synthesis, cell growth, and viability in response to cellular energy levels.

Clinical Highlight: Camfield P, Camfield C, Lortie A, Darwish H (2003) **Infantile spasms in remission may reemerge as intractable epileptic spasms.** *Epilepsia* 44(12):1592-5

Abstract: West syndrome consists of infantile spasms with hypsarrhythmia and is perceived as a disorder of infants. Methods: This study, carried out at Dalhousie University and the IWK Grace Health Centre, Halifax, Nova Scotia University of Montreal and Ste. Justine Hospital, Montreal, Quebec University of Calgary and the Alberta Children's Hospital, Calgary, Alberta, Canada, describes 10 patients with West syndrome with spasms that remitted, started again, and persisted (followed up for 8-25 years). In all, West syndrome developed at younger than 17 months (five cryptogenic, six symptomatic). With initial treatment, spasms completely stopped for 4.5 months to 6 years, when epileptic spasms returned. Recurrent spasms were typical with brief arm extension, eye elevation, and head drop without falling. Spasms lasted 2-6 s in rhythmic strings over 20- to 60-min periods and occurred daily throughout follow-up. Persistent spasms were particularly troublesome, because of incontinence in one and postictal confusion in several. During the string of spasms, most refused to interact, and several would wander off. Up to 15 antiepileptic drugs did not render any patient spasm free. Only two had persistent spasms as the only seizure type; six also had intractable complex partial seizures, and three had occasional grand mal convulsions. Interictal EEGs showed multifocal spikes. Ictal recordings in six

showed electrodecremental events. Conclusions: Recurrent spasms after remission of West syndrome represent an extremely resistant, distressing form of epilepsy. The onset of West syndrome is age related, but it does not reliably vanish.

New Publications

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