



TSC ALERT

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February/March 2004

Welcome to the February/March 2004 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 April 2004 *TSC Alert* contact: Vicky.Whittemore@tsalliance.org

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IMPORTANT DEADLINES:

April 2, 2004: Extended deadline for submission of abstracts for upcoming International TSC Conference in Cambridge, UK. See Tuberous Sclerosis Association Web site for additional information and forms at: <http://www.tuberous-sclerosis.org/research/conference/index.shtml>

For any queries please contact Ann Hunt at: research@tuberous-sclerosis.org
or telephone/fax: 44 (0)1993 881238

May 4, 2004: Deadline for submission of grant applications for the Tuberous Sclerosis Complex Research Program (TSCR) through the Congressionally Directed Medical Research Program. Applicants do not have to be U.S. citizens or perform research in the U.S. in order to apply for funding. See information below, or on the Web site at:
<http://cdmrp.army.mil/funding/04tsrp.htm>

GRANT ANNOUNCEMENTS:

Department of Defense Tuberous Sclerosis Complex Research Program Funding Opportunities for Fiscal Year 2004

Deadline: May 4, 2004

This year the TSCR will provide three funding mechanisms for all research on TSC. They are:

- **Concept Awards:** The intent of the Concept Award is to fund the exploration of an initial concept or theory that could give rise to a testable hypothesis. These awards are to encourage the exploration of untested, high-risk questions relevant to Tuberous Sclerosis and are not intended to support the next step in an already established research project. Presentation of preliminary data is not consistent with the intent of this award mechanism.
- **Idea Development Awards:** Idea Development Awards are intended to encourage innovative research directed toward improved prevention, diagnosis, and/or treatment of tuberous sclerosis. All Idea Development Award proposals *must include preliminary data* relevant to tuberous sclerosis research and the proposed project.
- **Natural History Development Awards:** The intent of Natural History Development Award is to provide support for the development of a multi-institutional natural history study that will ascertain and analyze sufficient numbers of patients with tuberous sclerosis (TS) to yield a substantial normative data set and provide quantitative data on TS-related tumor growth and/or other manifestations of TS. The Natural History Development Award proposal should include plans for the establishment of the research team, the development of tools for data management and trial/research administration, the definition of recruitment strategies, and the development of the clinical protocol and other essential components of the study included in a Manual of Operations and Procedures. An additional goal of these awards is the formation of a consortium of investigators with the potential to carry out clinical trials and to expand cooperative research into the various clinical manifestations of this disease.

For more information, visit the CDMRP website at: <http://cdmrp.army.mil>

Bernard D'Souza International Fellowship Award

Deadline: May 1, 2004

The Child Neurology Society is now accepting applications for the 2004 Bernard D'Souza International Fellowship Award, which will sponsor all expenses for a child neurologist from a developing country to attend the 33rd Meeting of the CNS to be held in Ottawa, Canada, October 13-16, 2004. This will be preceded, or followed, by a visit to a selected training program in North America. The purpose of the award is to promote child neurology in developing countries. Applicants must have trained in a developing country, should be practicing child neurology in an academic environment and should be prepared to present a scientific paper in English. Preference will be shown to applicants less than age 45 years.

The deadline for receipt of applications for the award is **May 1, 2004**. The application and complete selection criteria can be obtained by contacting:

Geoffrey Miller, M.D.
Chair, International Affairs Committee
Child Neurology Society
Neurology Section
Texas Children's Hospital
6621 Fannin, CC1710
Houston, Texas 77030
Phone: 832-822-1779
Fax: 832-822-1717
E-mail: gmillers@bcm.tmc.edu

LAM Foundation Postdoctoral Fellowships

Deadline: September 1

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, Lymphangiomyomatosis (LAM.) The LAM Post Doctoral 3 year Fellowship Awards provide a maximum of \$150,000 (\$50,000 per year, renewable for up to two additional years). Pilot Project Awards of up to \$25,000 are also available for the initiation of innovative research projects. Candidates must have at least two years of experience, an MD, PhD, or equivalent degree, and perform the work in a laboratory with established expertise in smooth muscle biology or the genetics of tuberous sclerosis. Examples of competitive proposals include those that focus on the genetic regulation of smooth muscle growth or the development of a smooth muscle cell line that is representative of LAM lesion. Mechanistic, hypothesis driven approaches of all types are welcomed. Formalin-fixed LAM tissues, dispersed LAM lung cells, genetic probes and other reagents are available. The deadline for fall applications is **September 1st** and funding begins January 15th of the following year. You may write to The LAM Foundation at 10105 Beacon Hills Drive, Cincinnati, Ohio, 45241 or email lam@one.net. For your convenience, you will find the terms and application form under [Funding for Scientists](#) on the LAM Foundation Web site.



NIH ANNOUNCEMENTS:

NIH Director's Pioneer Award

<http://www.nihroadmap.nih.gov/highrisk/initiatives/pioneer/>

ELSI Small Grant Research Program (R03) PA-04-051

<http://grants.nih.gov/grants/guide/pa-files/PA-04-051.html>

ELSI Regular Research Program (R01) PA-04-050

<http://grants.nih.gov/grants/guide/pa-files/PA-04-050.html>

NIDCD SMALL GRANT (R03) PROGRAM PAR-04-062

National Institute on Deafness and Other Communication Disorders
INDEX: DEAFNESS, OTHER COMMUNICATION DISORDERS
APPLICATION RECEIPT DATE(S): Multiple dates, see announcement
<http://grants.nih.gov/grants/guide/pa-files/PAR-04-062.html>

DEVELOPMENTAL MECHANISMS OF HUMAN STRUCTURAL BIRTH DEFECTS PA-04-052

National Institute of Child Health and Human Development
APPLICATION RECEIPT DATE: Multiple dates, see announcement
<http://grants.nih.gov/grants/guide/pa-files/PA-04-052.html>

Molecular Libraries Small Molecule Repository Amendment 1 RM-04-0001

(*pdf format, 9 pages)
<http://www.nlm.nih.gov/grants/Amend01RM040001.pdf>

7th Annual NIMH Research Roundtable

(*pdf format, 20 pages, 1,012 KB)
<http://www.nlm.nih.gov/research/roundtable2003reporta.pdf>

National Advisory Mental Health Council

Feb. 6 Open Policy Session Agenda (*pdf format)
http://www.nlm.nih.gov/council/policyagenda_feb04.pdf

ANNOUNCING 2004 NIH REGIONAL SEMINARS IN PROGRAM FUNDING AND GRANTS ADMINISTRATION (NOT-OD-04-018)

National Institutes of Health
<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-018.html>

THE SPECIALIZED CENTERS OF RESEARCH ISSUES REPORT

The Specialized Centers of Research (SCOR) Program Review Committee (a group of 8 outside experts) has submitted its final report to the NIAMS Director and to the NIAMS Council.

The Institute is now soliciting comments broadly from lay and professional communities for the next 8 weeks, and we would encourage you to distribute this to anyone who might be interested in commenting.

To view the message from Dr. Katz and the Report as well as to provide comments, please visit http://www.niams.nih.gov/ne/reports/sci_wrk/index.htm.

TSC TISSUE AVAILABILITY:

If you are interested in obtaining tissue for your research, please contact the Brain and Tissue Bank at 1-800-847-1539 or visit their Web site at: <http://som1.umaryland.edu/braintissuebank>

If you have specific needs for TSC tissue for your research, please contact Vicky Whittemore at vwhittemore1@comcast.net

RESOURCES:

Tsc2+/- MICE NOW AVAILABLE FROM JACKSON LABS

Tsc2+/- mice are now available from Jackson Labs. For those interested in obtaining the animals, refer to Stock #004686 B6;129S4-Tsc2<tm1Djk>/J. For licensing and technical

information please refer to the strain data sheet at:
<http://jaxmice.jax.org/micedata.shtml?stock=004686>

NEWS:

IMPORTATION OF MEDICATIONS TO THE UNITED STATES - "Coverage of Personal Importations" The FDA has developed guidance entitled "Coverage of Personal Importations" which sets forth that agency's enforcement priorities with respect to the personal importation of unapproved new drugs by individuals for their personal use. The guidance identifies circumstances in which FDA may consider exercising enforcement discretion and refrain from taking legal action against illegally imported drugs. Those circumstances are as follows:

- "1) the intended use [of the drug] is unapproved and for a serious condition for which effective treatment may not be available domestically either through commercial or clinical means;
- 2) there is no known commercialization or promotion to persons residing in the U.S. by those involved in the distribution of the product at issue;
- 3) the product is considered not to represent an unreasonable risk; and
- 4) the individual seeking to import the product affirms in writing that it is for the patient's own use (generally not more than a 3 month supply) and provides the name and address of the doctor licensed in the U.S. responsible for his or her treatment with the product, or provides evidence that the product is for the continuation of a treatment begun in a foreign country."

Customs may or may not stop the medication at the border, especially in light of the recent increase in the number of prescription medications being imported from Canada simply because they are cheaper. The consumer may want to notify customs that they are expecting the shipment of medication coming through, and tell them what the medication is going to be used for. Additional information can be obtained on the FDA website at:
http://www.fda.gov/ora/import/ora_import_program.html

HHS NAMES MEMBERS TO TASK FORCE ON DRUG IMPORTATION HHS Secretary Tommy G. Thompson today named 13 people to serve on the new Task Force on Drug Importation that is exploring how drug importation might be conducted safely and its potential impact on the health of American patients, medical costs and the development of new medicines. Surgeon General Richard H. Carmona will serve as the task force's chairman. The panel includes representatives from across HHS, as well as from other parts of the federal government with knowledge or involvement in drug importation issues. The task force may consult other federal officials as well. Secretary Thompson also announced the dates for the task force's five listening sessions with groups and individuals who would be affected by drug importation. The first meeting will take place Friday, March 19, and will feature speakers from at least a dozen invited consumer groups. The dates of the other listening sessions are: April 2 with health care purchasers; April 28 with professional health care providers; May 6 with industry representatives; and May 14 with international stakeholders. In addition, the task force will hold a public hearing on April 14 to allow members of the general public to present their views on the issue. The hearing will take place in the Natcher Auditorium at HHS' National Institutes of Health in Bethesda, Md. Information about participating in the public hearing is available at
<http://www.fda.gov/OHRMS/DOCKETS/98fr/04n-0115-nm00001.pdf>

HHS ESTABLISHES NEW ADVISORY COMMITTEE ON HERITABLE DISORDERS AND GENETIC DISEASES IN NEWBORNS AND CHILDREN HHS Secretary Tommy G. Thompson appointed 15 members to a new Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. Heritable disorders are passed from parents to children; many such disorders are treatable if detected early.

The committee will make recommendations to the Secretary on grants and projects to help states and local public health agencies improve screening, counseling and health care services to newborns and children who have or are at risk for heritable disorders. Committee members will also advise the Secretary on policies and priorities to help agencies provide these services.

Established in 2003 to review screening practices for genetic diseases, the committee – including medical doctors, geneticists and a parent/health care consultant – will consider the most appropriate application of universal newborn screening tests, technologies and guidelines. Title XXVI of the Children's Health Act of 2000 established a program to support states in providing screening to reduce death and disease related to heritable disorders in newborns and children. The committee will be chaired by R. Rodney Howell, M.D., Ph.D., chairman, Department of Pediatrics, University of Miami School of Medicine and chief of pediatrics, Jackson Children's Hospital, Miami.

SENDING CANCER A SUICIDE NOTE Researchers have dreamed of thwarting cancer by using proteins that halt cell growth and kill the tumor. In theory, the approach should work. In practice, however, scientists have not had an easy time of getting tumor suppressor proteins into cells where they can block growth effectively. Now, those barriers are crumbling thanks to an ingenious technique engineered by HHMI researcher, Steven F. Dowdy, Ph.D., University of California, San Diego, who have figured out a way to send tumors a genetic suicide note. For the full story, go to <http://www.hhmi.org/news/dowdy2.html>

RESEARCHERS ADAPT RNA INTERFERENCE TO STUDY GENE FUNCTION ON A LARGE SCALE Howard Hughes Medical Institute (HHMI) researcher Norbert Perrimon, Ph.D. and colleagues from Harvard Medical School, are developing and piloting a method for determining the function of large numbers of genes. In a trial of the technique, the researchers characterized the role in growth and viability of nearly all the genes in the genome of the fruit fly, *Drosophila*. This research was published in the February 6, 2004, issue of *Science*. For the full story, go to <http://www.hhmi.org/news/perrimon2.html>

TECHNIQUE EAVESDROPS ON THE "INNER LIFE" OF PROTEINS Howard Hughes Medical Institute researchers David J. Mangelsdorf, Ph.D., University of Texas Southwestern Medical Center at Dallas and Rama Ranganathan, M.D., Ph.D., University of Texas Southwestern Medical Center at Dallas have developed an analytical technique that can be used to reveal the amino acids that are critical links in the internal communications network of proteins. This research was published in the February 6, 2004, issue of *Cell*. For the full story, go to <http://www.hhmi.org/news/sca.html>

NEW RNA LIBRARIES CAN INACTIVATE HUMAN GENES SELECTIVELY HHMI researcher, Stephen J. Elledge, Ph.D., Brigham and Women's Hospital, and their colleagues have produced vast libraries of short segments of ribonucleic acid (RNA) that can be used to turn off individual human and mouse genes to study their function. The libraries will be made widely available to laboratories studying human biology and disease. The researchers are optimistic that the libraries will become a powerful research tool for gene analysis and discovery. This research was

published in the March 25, 2004, issue of Nature. For the full story, go to <http://www.hhmi.org/news/elledge3.html>

CELLS INDUCED TO “DE-DIFFERENTIATE” BACK TO STEM CELLS Researchers have induced differentiating cells to revert back to stem cells. Their achievement with the fruit fly suggests that de-differentiation should be explored as a route to generating stem cells for therapeutic purposes. Research by Allan C. Spradling, Ph.D., Carnegie Institution of Washington, was published in the March 14, 2004, issue of Nature. For the full story, go to <http://www.hhmi.org/news/spradling2.html>

FOGARTY INTERNATIONAL CENTER ANNOUNCES FIRST AWARDS FOR COLLABORATIVE RESEARCH PROGRAM FOR BRAIN DISORDERS IN THE DEVELOPING WORLD The Fogarty International Center (FIC) of the National Institutes of Health (NIH) and eight NIH partners* announce 31 new research planning grants to support international collaborations to study brain disorders in developing countries. The current combined financial commitment from FIC and its partners for the first phase of this program is approximately \$8.1 million to support these two-year grants.

This new program grew out of the recognition of the enormous global burden of disease posed by mental illness and a variety of conditions affecting brain function, or brain disorders for short. Currently, brain disorders are responsible for 27 percent of all years lived with disability (YLDs) in developing countries and, with the exception of Sub-Saharan Africa, are the leading contributors to YLDs in all regions of the world.

In the design phase, FIC convened a consultation of experts, led by Nobel Laureate Torsten Wiesel, with significant representation from developing countries, to discuss challenges and opportunities for scientific study in this field. Areas considered, now integral to the program, included research, and training in developmental brain disorders, epilepsy, neurological trauma and injury, schizophrenia and depression, and acquired cognitive disorders of adults, including dementia due to HIV infection and other causes.

"The suffering from brain disorders and mental illness, along with their concomitant social and economic impacts strain individuals as well as entire families, diminishing productivity and quality of life for all members," said FIC Acting Director Dr. Sharon Hrynkow, on behalf of the partners. "While cost-effective treatments to reduce the burden of certain brain disorders, including epilepsy, schizophrenia and depression, are available in the developed world, this is not the case in the developing world. This program will support research on brain disorders and mental illness to develop new interventions that will benefit low-income populations around the world, and particularly in developing countries." Dr. Hrynkow added, "advances made along this line hold promise for interventions available more broadly, including here at home."

Each of the new projects will assess needs, develop collaborations and necessary resources, carry out feasibility and pilot studies, and put the necessary elements in place to create a strong collaborative research project that will contribute to the long-term goal of building sustainable research capacity in neurological/neurodevelopmental impairment. FIC anticipates that at the end of two years, an RFA will be issued to solicit applications for R01 research projects, which will be open to all applicants.

*NIH partners are the National Institute on Aging, National Institute on Alcohol Abuse and Alcoholism, National Institute of Child Health and Human Development, National Institute on Drug Abuse, National Institute of Environmental Health Sciences, National Institute of Mental

Health, National Institute of Neurological Disorders and Stroke and the Office of Dietary Supplements.

The following studies may be of interest to TSC researchers and clinicians:

Dr. Elena Grigorenko, Yale University, and colleagues at the University of Zambia are collaborating on a study that will establish a network of Zambian and international researchers to conduct future large scale epidemiological studies of learning disabilities in Zambia. Dr. Penny Holding, Kenya Medical Research Institute, will work with researchers at City University, London, United Kingdom to develop a measure of brain insults in Kenyan children. The investigators will monitor and evaluate the psychomotor development of infants and young children to provide scientists in East Africa with a methodology for the investigation of the sequelae of brain disorders of pre-natal and peri-natal origin.

Dr. Ann Jacoby, University of Liverpool, and colleagues at Beijing Neurological Institute, China, the World Health Organization, and the Hanoi School of Public Health in Vietnam on a study that aims to understand and reduce the stigma surrounding people with epilepsy in China and Vietnam.

Dr. Annette Karmiloff-Smith, University of London Institute of Child Health, will collaborate with colleagues at Zhejiang University, China, and University College London, UK on a project whose goal is to develop a collaborative research program on cognitive and brain phenotypes of mentally retarded Chinese children with genetic disorders (Fragile-X syndrome, Williams syndrome, and Down syndrome). Dr. John Leventhal, Yale University, will work with colleagues at Ankara University, Turkey on a collaboration that aims to develop infrastructure and strengthen the capacity to conduct research in Turkey on the recognition, prevention and treatment of developmental problems and disabilities in infants, young children and their families.

Dr. Laurie Miller, New England Medical Center Hospitals, will work with researchers at Murmansk Children's Hospital in Russia on a project that looks at neurodevelopmental outcomes in Russian orphanages. The study will explore the contributions of the environment in promoting optimal brain development in young children and will be part of the development of a center for training in evidence-based research to prevent and reduce developmental disabilities among these children.

Dr. Craig Newschaffer, Johns Hopkins University, is working with colleagues at Peking University, Beijing, China and The Kennedy Krieger Institute, Baltimore, Maryland on a study that aims to build collaborations and research capacity around the conduct of epidemiological research of autism spectrum disorders in China.

FIC is the international component of the NIH. It promotes and supports scientific discovery internationally and mobilizes resources to reduce disparities in global health. NIH is an agency of the U.S. Department of Health and Human Services. Press releases and other FIC-related materials are available at <http://www.fic.nih.gov>

**INTERNATIONAL SEQUENCING CONSORTIUM LAUNCHES ONLINE RESOURCE
New Web Site Promotes Sharing of Large-Scale Sequencing Information**

The International Sequencing Consortium (ISC) has launched a free, online resource where scientists and the public can get the latest information on the status of sequencing projects for animal, plant and other eukaryotic genomes, the National Human Genome Research Institute (NHGRI) announced today. The new resource can be accessed through ISC's home page,

<http://www.intlgenome.org> The database enables users to quickly sort sequencing project information by organism, by sequencing group or by funding agency.

TRANSGENIC ANIMALS PRODUCED USING CULTURED SPERM: Study Opens New Possibilities for Biological Research, Gene Therapy A Japanese-U.S. team reported the successful creation of transgenic animals using sperm genetically modified and grown in a laboratory dish, an achievement with implications for a wide range of research from developmental biology to gene therapy.

In their study, to be published in the online edition of the "Proceedings of the National Academy of Sciences" during the week of Jan. 26-30, researchers from Fukui Prefectural University in Obama, Japan, and the National Human Genome Research Institute (NHGRI), which is part of the National Institutes of Health (NIH), describe the innovative techniques they used to produce genetically modified zebrafish using sperm cells grown under laboratory, or "in vitro," conditions.

"To our knowledge, this is the first time that sperm cells have been cultured entirely "in vitro" and used to produce a transgenic animal. It was a unique challenge that required creative solutions," said Shawn Burgess, Ph.D., an investigator in NHGRI's Genome Technology Branch and a co-author of the study.

Although further refinement and testing is needed, Dr. Burgess said the new techniques have the potential to speed the production of many different types of transgenic animal models that will shed new light on human development and disease. The sperm culturing system will allow researchers to further explore the basic biology of sperm production in vertebrates. The findings also may prove helpful to researchers exploring pre-fertilization strategies for human gene therapy, thus allowing preventive treatment for certain genetic disorders, Dr. Burgess said.

Eric D. Green, M.D., Ph.D., NHGRI's scientific director and director of the Division of Intramural Research, said, "This is an outstanding example of our efforts to build upon the foundation laid by the Human Genome Project. Development of such novel technologies and methods will be essential for translating our rapidly growing knowledge of the genetic basis of disease into better diagnostic approaches and therapeutic options."

Past efforts to genetically modify sperm cells in animals prior to fertilization have been stymied by the failure of these cells to mature under "in vitro" growth conditions. Drawing upon the cell culture expertise of Noriyoshi Sakai, Ph.D., and Kayoko Kurita, of Fukui Prefectural University, the Japanese-U.S. team developed a system that enables immature sperm cells, or spermatogonia, taken from male zebrafish to survive long enough "in vitro" that they can receive foreign genes inserted by a retrovirus. Those cells go on to develop into mature, functional sperm. The genetically modified, cultured sperm are then used to fertilize zebrafish eggs in a laboratory dish -- a process known as "in vitro" fertilization -- resulting in the production of transgenic embryos and, ultimately, transgenic zebrafish.

"The secret to our success was the idea of placing a layer of special 'feeder cells' under the spermatogonia in the laboratory dish. These feeder cells, derived from zebrafish testicular cancer cell lines, promote the growth of spermatogonia and stimulate them to mature into functional sperm," said Dr. Sakai, the study's senior author and a reproductive biologist.

One of the biggest advantages of the cultured sperm approach is that transgenic zebrafish created in this way carry the inserted, foreign gene in every cell of their bodies, including their germ cells. This means the fish will transmit the foreign gene along to their offspring in a pattern identical to their natural genes.

"Conventional techniques of producing transgenic animals, such as microinjection of genes into eggs and the retroviral transduction of genes into embryos, often produce many animals that are mosaic, which means they do not contain the foreign gene in all their cells. In the case of zebrafish, less than 20 percent of fish produced by injecting DNA into fertilized eggs will transmit the foreign gene to the next generation. So, we have to sort through hundreds of fish and breed them for two generations to produce a stable, transgenic line," said Dr. Burgess. "With the new approach, the transgenic fish are not mosaic, so screening for transgenics is reduced and an entire generation of breeding is skipped. That saves significant time and money."

The zebrafish, "Danio rerio", is a small, transparent aquarium fish used as a model system for studying the biology of vertebrates. The fish, which share many of the same genes as humans, are ideal for genetic studies because of their rapid rate of reproduction and because their genes can be readily mutated. However, researchers have been frustrated by the lack of methods to target mutations to specific genes in the zebrafish.

In their current system, the researchers can grow zebrafish sperm cells in culture for about 12 days. According to Dr. Burgess, the team is now working to extend the period that sperm cells can be cultured, so there is more time to select cells that have the foreign gene inserted in specific areas of the genome in what is commonly called a "targeted gene knockout". Currently, such gene targeting is not possible in zebrafish or any vertebrate animal model system other than mice, for which such targeting involves the use of embryonic stem cells.

NHGRI is one of the 27 institutes and centers at NIH, an agency of the Department of Health and Human Services. The NHGRI Division of Intramural Research develops and implements technology to understand, diagnose and treat genomic and genetic diseases.

Additional information about NHGRI can be found at its Web site, <http://www.genome.gov>

MONKEY TALK, HUMAN SPEECH SHARE LEFT-BRAIN PROCESSING Scans have pinpointed circuits in the monkey brain that could be precursors of those in humans for speech and language. As in humans, an area specialized for processing species-specific vocalizations is on the left side of the brain, report Drs. Amy Poremba, Mortimer Mishkin, and colleagues at the National Institute of Mental Health (NIMH), Warren G. Magnuson Clinical Center (CC), components of the National Institutes of Health (NIH), and the University of Iowa. An area near the left temple responded significantly more than the same area on the right only to monkey calls, not to other animal calls, human voices or various other sounds. The researchers published their findings in the January 29, 2004 "Nature".

"Since it's in the left temporal lobe and specialized for vocalizations only, it bears intriguing similarities to human language," noted Mishkin. "Assuming this is an adaptive mechanism, it suggests that vocalizations can be deciphered better if they are processed by only one temporal pole rather than by both."

Scientists have known for years that the human brain processes speech on the left side of the brain, but they only had hints that this is also the case for non-human primates. For example, when a monkey hears a call from behind, it characteristically turns its head to the right, suggesting that the primitive vocalizations are being processed in the left hemisphere, which receives greater input from the right ear than from the left. Also, a monkey's ability to perceive such calls is impaired if it lacks the left auditory cortex, but not the right.

To find out how this works, the researchers used PET (positron emission tomography) scanning

(<http://www.nimh.nih.gov/hotsci/petscan.htm>). A radioactive tracer visualized the parts of the brain that were active while different types of sounds were being processed. After eight healthy monkeys heard a series of monkey calls, an area just below the left temple, at the front of the left temporal lobe (left dorsal temporal pole), activated significantly more than its mate on the right. Yet, this area failed to similarly activate when the animals heard a variety of other sounds - bells, tones, dog barks, bird tweets, a human voice, scrambled monkey calls, etc. Instead, significant activation was seen in a different temporal lobe area on the right side of the brain, which seems to process virtually every sound.

To gain insight into how the brain achieves this hemispheric specialization, three monkeys surgically-altered to lack connecting links between the hemispheres were also scanned after listening to the sounds. With communication between the hemispheres severed, the asymmetrical pattern vanished. Conspicuously, no significant difference in activation was seen in the two temporal poles when the animals heard monkey calls.

This suggests that monkey calls normally stimulate interactions between brain hemispheres that suppress the corresponding right temporal lobe area, focusing auditory processing within the left area. "Our results open up the possibility of characterizing such neuronal responses in a cortical region of the monkey that is not only a higher-order auditory processing area, but also one that could be a precursor for an acoustic language area in humans," note the researchers.

"This study provides neuroscientists with new biological clues for studying how communication evolved," said Poremba, who left NIMH a few years ago and is now at the University of Iowa. In addition to NIMH, the research was supported, in part, by the University of Iowa. Also participating in the study were Megan Malloy, NIMH, Dr. Richard Saunders, NIMH, Dr. Richard Carson, CC, Dr. Peter Herscovitch, CC.

Graphics are available online at <http://www.nih.gov/news/pr/jan2004/nimh-29.htm#graphics>

NEW TSC PUBLICATIONS:

TSC Basic Science Highlight: Han S, Santos TM, Puga A, Roy J, Thiele EA, McCollin M, Stemmer-Rachamimov A, Ramesh V (2004) Phosphorylation of tuberin as a novel mechanism for somatic inactivation of the tuberous sclerosis complex proteins in brain lesions. *Cancer Res* 64(3):812-6

Tuberous sclerosis complex (TSC) is caused by mutations in the tumor suppressor genes TSC1 or TSC2, and is characterized by the presence of hamartomas in many organs. Although TSC is a tumor suppressor gene syndrome with classic "second hits" detectable in renal tumors, conventional genetic analysis has not revealed somatic inactivation of the second allele in the majority of human brain lesions. Han and coworkers (2004) demonstrate a novel mechanism of post-translational inactivation of the TSC2 protein, tuberin, by physiologically inappropriate phosphorylation, which is specific to TSC-associated brain lesions. Additional analysis shows that tissue specificity is due to abnormal activation of the Akt and mitogen-activated protein kinase pathways in brain but not in renal tumors. These results have widespread implications for understanding the tissue specificity of tumor suppressor gene phenotypes.

TSC Clinical Science Highlight: Lazarowski A, Lubieniecki F, Camarero S, Pomata H, Bartuluchi M, Seveler G, Taratuto AL (2004) Multidrug resistance proteins in tuberous sclerosis and refractory epilepsy. *Pediatr Neurol* 30(2):102-6

Tuberous sclerosis complex (TSC) is an autosomal dominant syndrome characterized by seizures that are refractory to medication in severely affected individuals. The mechanism involved in drug

resistance in TSC is unknown. The proteins MDR-1 (multidrug resistance) and MRP-1 (multidrug resistance-associated protein-1) are linked to chemotherapy resistance in tumor cells. However, the relationship between refractoriness to antiepileptic drugs and MDR-1 or MRP-1 brain expression has been poorly studied. Lazarowski and coworkers (2004) previously described a case of TSC with refractory epilepsy that expressed multidrug resistance gene (MDR-1) in tuber cells from epileptogenic brain lesion. In this retrospective study, they describe the expression of MDR-1 and MRP-1 in the epileptogenic cortical tubers of three pediatric patients with TSC and refractory epilepsy surgically treated. Monoclonal antibodies for MDR-1 and MRP-1 proteins were used for immunohistochemistry. In epileptogenic cortical tuber brain specimens, MDR-1 and MRP-1 proteins were strongly immunoreactive in abnormal balloon cells, dysplastic neurons, astrocytes, microglial cells, and some blood-brain vessels. A more extensive MDR-1 immunoreactivity was observed. These data suggest that refractory epilepsy phenotype in TSC can be associated with the expression of both multidrug resistance MDR-1 and MRP-1 transporters in epileptogenic cortical tubers.

New TSC References:

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