Welcome to the February 2005 edition of *TSC Alert* – an online research newsletter for individuals interested in Tuberous Sclerosis Complex (TSC) research and clinical care. This online newsletter contains information of interest to the TSC research and health care community. Please forward this newsletter to colleagues who are interested in TSC. To be added/deleted to/from the mailing list for *TSC Alert* and/or to submit information for the March 2005 *TSC Alert* contact: Vicky.Whittemore@tsalliance.org

**Table of Contents**

[Clicking on one of the headings takes you directly to that section of TSC Alert]

- IMPORTANT DEADLINES .................................................................................................................1
- GRANT ANNOUNCEMENTS .............................................................................................................2
- NEW TSC PUBLICATIONS ................................................................................................................5
- CONFERENCES .................................................................................................................................7
- NEWS ................................................................................................................................................9
- TSC INFORMATION ..........................................................................................................................18

**IMPORTANT DEADLINES**

**TSC/LAM International Research Symposium – Call for Abstracts!**
Deadline for submission of Late-breaking Abstracts: March 15, 2005
Deadline for Early Registration: February 18, 2005
(See information below in Conferences)

**TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM (TSCR) IN THE CDRMP**
Deadline: February 22, 2005
(See information below in Grant Announcements)
**Eppendorf & Science Prize for Neurobiology - $25,000 Prize for Neurobiology**
Now accepting entries for the $25,000. Deadline is June 15, 2005.

**GRANT ANNOUNCEMENTS**

**TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM (TSCRP) IN THE CDRMP**
**Deadline: February 22, 2005**
The Fiscal Year 2005 (FY05) Defense Appropriations Act provides $3.2 million to the Department of Defense Tuberous Sclerosis Complex Research Program (TSCRP) to support innovative research directed toward improved prevention, diagnosis, and treatment of TSC. This program is administered by the US Army Medical Research and Materiel Command through the Office of the Congressionally Directed Medical Research Programs (CDMRP). The deadline for the receipt of electronic submissions is February 22, 2005 at 5:00 p.m. Eastern time.

FY05 TSCRP Program Announcements for the following mechanisms can be found on the DCMRP Web site.

- Natural History Study Awards - New
- Natural History Development Awards
- Concept Awards
- Idea Development Awards

Detailed descriptions of each mechanism are provided in the FY05 TSCRP Program Announcements on the DCMRP Web site. For more information about the TSCRP or other CDMRP-sponsored programs, please visit the CDMRP website at: [http://cdmrp.army.mil/funding/05tscrp.htm](http://cdmrp.army.mil/funding/05tscrp.htm)

**HHMI, EMBO to Offer 3-Year, $75,000 Grants to Young Investigators in Central Europe**
*By a GenomeWeb staff reporter*

NEW YORK, Feb. 10 (GenomeWeb News) - The Howard Hughes Medical Institute and the European Molecular Biology Organization will accept applications this week for the first of their annual $75,000 grants, which aim to encourage young scientists to establish laboratories in Central Europe, the organizations said yesterday.

The 3-year grants EMBO/HHMI Startup Grants are intended to support the acquisition of "equipment, supplies, personnel, space, and time" by scientists setting up in Croatia, Czech Republic, Estonia, Hungary, Poland, and Slovenia, the statement said.

The European Molecular Biology Organization will oversee the grants as part of its Young Investigator Program, and, along with member countries, it will contribute $25,000 per year for three years for a maximum of six grants. The remaining $50,000 for each of the six grants will come from HHMI, which is funding the effort as part of its international scholars program.

Scientists have until Aug. 1 to apply for the grants with research institutes in the participating countries. As part of the grants, applicant institutes are asked to commit to guarantee long-term support of the young investigators.
Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) to Improve The Chemistry and Targeted Delivery of RNAi Molecules (PA-05-041)
National Institute of Neurological Disorders and Stroke
National Cancer Institute
National Center for Research Resources
National Human Genome Research Institute
National Heart, Lung, and Blood Institute
National Institute on Aging
National Institute of Allergy and Infectious Diseases
National Institute of Biomedical Imaging and Engineering
National Institute on Drug Abuse
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of General Medical Sciences
National Institute of Mental Health
Application Receipt Date(s): Multiple dates, see announcement.

Directed Stem Cell Differentiation for Cell-Based Therapies for Heart, Lung, and Blood, and Aging Diseases (R21) (PA-05-043)
National Heart, Lung, and Blood Institute
National Institute on Aging
Application Receipt Date(s): Multiple dates, see announcement.

Directed Stem Cell Differentiation for Cell Based Therapies for Heart, Lung, Blood, and Aging Diseases (SBIR/STTR) (PA-05-044)
National Heart, Lung, and Blood Institute
National Institute on Aging
Application Receipt Date(s): Multiple dates, see announcement.

Mechanisms of Adverse Drug Effects in Children (PA-05-045)
National Institute of Child Health and Human Development
Application Receipt Date(s): Multiple dates, see announcement.

Research Award Application Deadline: 6:00 pm CST March 7, 2005
The James S. McDonnell Foundation (JSMF) announces updated program descriptions and application guidelines for its 21st Century Science Initiative Research Awards. The 21st Century Research Awards support investigator-initiated research. Funding is available for research projects in Brain Cancer; Bridging Brain, Mind, and Behavior; and Studying Complex Systems. Program information, application guidelines, and proposal preparation instructions are available at: http://www.jsmf.org. No geographic restrictions; international applications are
encouraged. Information on the Foundation’s 21st Century Collaborative Activity Awards is also available on the website.

**K 23 with Emphasis on Therapeutic Interventions Employing Genomic or Proteomic Technologies (RFA-HG-05-013)**
National Human Genome Research Institute
National Institute on Drug Abuse
Office of Rare Diseases
Application Receipt Date(s): June 15, 2005

**Multidisciplinary Clinical Research Career Development Programs**
NIH has announced a multidisciplinary clinical research program on career development to support the early career development of clinical researchers expected to achieve excellence in their ability to design and oversee research in multidisciplinary team settings. Eligible principal investigators should have a strong and active track record in clinical research, clinical research training, and administration that demonstrates the skills, knowledge, and experience necessary to develop and manage the proposed career development program.

**Epilepsy Research Foundation: New Therapy Grants Program**
**Information for Applicants**  **APPLICATIONS DUE:** October 1, 2004 and April 1, 2005
The Epilepsy Research Foundation was created through a partnership between the Epilepsy Foundation and The Epilepsy Project. The mission of the Epilepsy Research Foundation is to fund new research avenues seeking a cure for epilepsy and to support the development of more effective therapies by serving as a catalyst for moving innovative therapies from the laboratory to the patient. The Epilepsy Research Foundation is committed to bringing about real research advances. http://www.epilepsyproject.org/sec/available_grants

**Epilepsy Foundation Funding Opportunity**
The Epilepsy Foundation invites applications for its Behavioral Sciences postdoctoral fellowships, behavioral sciences student fellowships, and health sciences student fellowships. The deadline for submission of applications is March 1, 2005. Funding of projects is to commence on July 1, 2005. Guidelines, including applications and deadlines, are available online. http://www.epilepsyfoundation.org/research/grants.cfm

**Assay Development for High Throughput Molecular Screening**
A component of the NIH Molecular Libraries and Imaging Roadmap Initiative, the Assay Development for High Throughput Molecular Screening is designed to facilitate the discovery of new molecular probes for investigating biological function by funding the development and adaptation of biological assays for automated high throughput molecular screening. Interested participants may submit more than one application. http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-05-011.html

**Innovative Therapies for Rheumatic and Skin Diseases** (NIH - NIAMS - BAA-05-01)
Proposal receipt date: March 25, 2005
**Early Therapeutics Development With Phase II Emphasis** (NOT-CA-05-014)
National Cancer Institute

**Risk of Disease in Hispanic Populations: Request for Information** (NOT-HL-05-105)
National Heart, Lung, and Blood Institute

**Animal Models of NIDDK-Relevant Diseases** (PA-05-049)
National Institute of Diabetes and Digestive and Kidney Diseases National Institute of Allergy and Infectious Diseases
Application Receipt Date(s): Multiple dates, see announcement.

**NEW TSC PUBLICATIONS**

**Journal of Child Neurology September 2004 Issue Focused on TSC**
The September 2004 issue of the Journal of Child Neurology, Vol. 19, Number 9, contains 15 articles on TSC that were presented at the 2003 Child Neurology Society meeting in the “Neurobiology of Disease in Children” Symposium organized by Bernard L. Maria, MD, MBA. E. Steve Roach, MD and David Gutmann, MD, PhD co-chaired the symposium. You may access the PDF of this issue on the Tuberous Sclerosis Alliance Web site at:

**Basic Science Spotlight:**


The inherently complex signaling networks of tumors result from genetic and epigenetic alterations that occur during cancer initiation and progression. In an attempt to identify early molecular changes associated with dominantly inherited predisposition to "two-hit" renal tumors, the expression profiles of primary cultures of phenotypically normal renal epithelial cells from individuals bearing a germline mutation in either the von Hippel-Lindau (VHL) or the tuberous sclerosis complex (TSC) gene were compared to that of renal epithelial cells from control nonmutation carriers by microarray analysis. Reliability of the microarray data from pooled samples was confirmed by real-time RT-PCR. Principal Component Analysis revealed substantial differences in the gene expression profiles of the renal epithelial cells from VHL and TSC mutation carriers. In several instances, the microarray data confirm our present knowledge of the cellular pathways affected by biallelic VHL and TSC mutations. These findings demonstrate that heterozygosity for a mutant tumor suppressor gene may alter the expression profiles of phenotypically normal epithelial cells in a gene-specific manner. Detectable effects of "one-hit" represent early molecular changes in tumorigenesis that may serve as targets for chemopreventive intervention.
Clinical Science Spotlight:


The purpose of this study was to use visual evoked potential (VEP) testing to determine whether visual deficits are present in children with a history of vigabatrin use. Contrast sensitivity and visual acuity were assessed by visual evoked potential testing and compared between 28 children (mean age, 4.90 +/- 4.92 years) with seizure disorders who had taken vigabatrin and 14 typically developing children (mean age, 3.14 +/- 1.70 years). Exclusion criteria were heritable eye disease, suspected cortical visual impairment, nystagmus, and prematurity >2 weeks. The effects of the following factors on contrast sensitivity and visual acuity were examined: type of seizure (infantile spasms versus other), ERG result, duration of vigabatrin therapy, cumulative dosage of vigabatrin, and other seizure medications (other versus no other medication). Contrast sensitivity and visual acuity were reduced in vigabatrin-treated children with infantile spasms compared with vigabatrin-treated children with other seizure disorders and typically developing control subjects. The other factors examined had no significant effect on contrast sensitivity or visual acuity, with adjustment for seizure type. Children with infantile spasms on vigabatrin may have compromised visual function, even in the absence of suspected cortical visual impairment. The present study found that the children tested have reduced vision, probably associated with infantile spasms rather than with vigabatrin use.

New TSC Publications:


CONFERENCES

**February 19-20, 2005**
**West Coast Regional TSC Conference**
Mission Inn, Riverside, CA
Sponsored and organized by the Community Alliance of the Tuberous Sclerosis Alliance
For more information and to register, visit the TS Alliance Web site at: [http://www.tsalliance.org](http://www.tsalliance.org)

**February 21-24, 2005**
**Twelfth International Symposium on Recent Advances in Drug Delivery Systems**
Grand America Hotel, Salt Lake City, UT
Register today at [www.pharmaceutics.utah.edu/cccd](http://www.pharmaceutics.utah.edu/cccd)

**February 22, 2005 (10:00 AM – 12:00 PM)**
**Genetic Nondiscrimination: 2005 Update**
Organized by the Coalition for Genetic Fairness
February 28 - March 1, 2005
Sixth Meeting of the Secretary’s Advisory Committee on Genetics, Health, and Society
Bethesda North Marriott Hotel, North Bethesda, MD
An agenda will be posted online a few weeks prior to the meeting at:

Public Comments: SACGHS welcomes public perspectives on any of the issues to be covered during the meeting as well as on issues important to members of the public. If you wish to provide comments at the meeting, please contact Amanda Sarata by email at sarataa@od.nih.gov or by phone at 301-496-9838 to sign up. Please indicate whether you will be speaking as an individual or on behalf of an organization, and if the latter, your affiliation with that organization. Public comments may also be submitted to SACGHS in writing via sarataa@od.nih.gov. In order to be considered by SACGHS at the February meeting, written comments should be submitted no later than February 24, 2005.

Meeting Logistics: The meeting is open to the public, and pre-registration is not required. Seating will be available on a first-come-first-serve basis.

For directions and to make online lodging reservations, please visit:
<http://marriott.com/property/propertypage/WASBN>

Webcast: The meeting will also be webcast. Information on how to gain access to the webcast will be available on the day of the meeting at:

Special Accommodations: Attendees requiring special accommodations, such as interpreting services, should contact Abbe Smith of Capital Consulting by phone at 301-468-6004 x402 or by email at asmith@md.capconcorp.com prior to the meeting.

April 8-10, 2005
TSC/LAM Research Conference & TSC Adult Conference
The Hyatt Regency, Downtown Cincinnati, OH
Organized by the Tuberous Sclerosis Alliance, LAM Foundation, and Rare Lung Disease Consortium

The Tuberous Sclerosis Alliance and the LAM Foundation invite you to attend the first joint TSC/LAM conference in Cincinnati, Ohio in April 2005. Sessions will include:

• The TSC Genes in the Brain – What Do They Do?
• Signaling Pathways and Basic Biology of TSC1/TSC2
• TSC-LAM Translational Research
• What Causes Epilepsy in TSC?
• Behavioral Phenotypes in TSC
• Late-Breaking Science and Roadmap for a Cure for TSC

CALL FOR LATE-BREAKING SCIENCE ABSTRACTS
Platform and poster presentations will be selected from submitted abstracts based on scientific merit and thematic considerations. The application and instructions may be completed
Deadline for submission of Late-Breaking TSC Abstracts: March 15, 2005
Deadline for Early Registration: February 18, 2005
For more information, Call for Abstracts, Agenda and Registration information: http://www.tsalliance.org

May 10-12, 2005
PharmaDiscovery
Washington, D.C. Convention Center
http://www.pharmadiscovery2005.com

June 21-22, 2005
National Summit on Preconception Care
The National Center on Birth Defects and Developmental Disabilities
Marriott Century Center, Atlanta, GA
Questions should be directed to Chris Parker via email at cparker@cdc.gov or telephone at (404)498-3098
Additional information and registration:

July 21-23, 2005
XXVII Annual Meeting of the Cognitive Science Society
Stresa, Italy
http://www.psych.unito.it/csc/cogsci05/home.html

September 11-14, 2005
The Second International Conference on Birth Defects and Disabilities in the Developing World
Jiuhua Spa and Resort, Beijing, China
www.chinamed.com.cn/birthdefects

Save the date! May 4-5, 2006
TSC International Research Conference 2006
Berlin, Germany
More information coming soon!

NEWS

CALL FOR SUBMISSIONS
JGIM SPECIAL ISSUE ON HEALTH LITERACY
The Society of General Internal Medicine (SGIM) invites submissions to a special issue of the Journal of General Internal Medicine (JGIM) on health literacy. Papers should be submitted online between now and June 30, 2005. Manuscripts will be reviewed by a team of experienced Co-Editors and peer reviewers. The goals of the theme issue are to 1) highlight
state of the art research and education related to the role of literacy in healthcare, 2) respond to the priority areas outlined in the Institute of Medicine report, *Health Literacy: A Prescription to End Confusion*, and 3) provide insight for clinicians, educators, researchers, administrators, and policy makers on addressing literacy in various healthcare settings.

**HHS ANNOUNCES SIMPLIFIED SYSTEM FOR RESEARCH PROTECTION ASSURANCES**

The U.S. Department of Health and Human Services (HHS) announced a new simplified mechanism for all research institutions that receive HHS funding or support to obtain an assurance of compliance with HHS regulations for the protection of human subjects. A single Web-based "Federalwide Assurance" (FWA) will replace the several types of assurances under which research institutions had operated in the past.

"We are pleased to provide this robust and flexible simplification to our assurance system," said Bernard A Schwetz, D.V.M., Ph.D., director of the Office Human Research Protection. "It reduces the burden of regulatory compliance while strengthening the research community's ability to focus on protections for research subjects."

Because of the multiple types of assurances in use, HHS will allow research institutions to transition to the new system over the next 11 months. By Dec. 31, 2005, all institutions conducting HHS-funded human subjects research must hold an FWA approved by HHS' Office for Human Research Protections (OHRP). For more information, visit the OHRP assurance Web page at [http://www.hhs.gov/ohrp/assurances/assurances_index.html](http://www.hhs.gov/ohrp/assurances/assurances_index.html).

Nearly all federal departments and agencies that conduct or fund human subject research adhere to the Federal Policy for the Protection of Human Subjects, a set of identical regulations adopted by 16 departments and agencies in 1991 that is known informally as the "Common Rule." The Common Rule is based on the HHS regulations in force since 1974 and requires that federally supported research involving human subjects be covered by an assurance. The other Common Rule agencies now have the option of using -- or directing their grantees to use -- the HHS FWA, rather than operating their own assurance systems, and a large majority of the agencies are expected to rely on the FWA.

The Common Rule signatories group includes the Departments of Agriculture, Energy, Commerce, Defense, Education, HHS, Housing and Urban Development, Justice, Transportation, Veterans Affairs, the Agency for International Development, the Central Intelligence Agency, the Consumer Products Safety Commission, the Environmental Protection Agency, the National Aeronautics and Space Administration and the National Science Foundation.

OHRP is a component of the Office of the Secretary, Office of the Assistant Secretary for Health, Office of Public Health and Science. OHRP works to support and strengthen the nation's system for protecting those who volunteer to participate in research that is conducted or supported by HHS agencies.

**Health Information: Child and Adolescent Mental Health**


**Antidepressant Medications for Children and Adolescents: Information for Parents and Caregivers**

INTERNATIONAL HAPMAP CONSORTIUM EXPANDS MAPPING EFFORT: Map of Human Genetic Variation Will Speed Search for Disease Genes

The International HapMap Consortium, boosted by an additional $3.3 million in public-private support, announced plans to create an even more powerful map of human genetic variation than originally envisioned. The map will accelerate the discovery of genes related to common diseases, such as asthma, cancer, diabetes and heart disease.

When the project was launched in October 2002, the consortium set September 2005 as the target for completing its map of common patterns of human genetic variation, also known as haplotypes. By the end of February 2005, however, the group already will have reached completion of its first draft of the human haplotype map, or HapMap, which will consist of 1 million markers of genetic variation, called single nucleotide polymorphisms (SNPs).

The consortium's new goal is to build an improved version of the HapMap that is about five times denser than the original plan. This "Phase II" HapMap will take advantage of the rapid, high-throughput genotyping capacity of Perlegen Sciences, Inc., of Mountain View, Calif., to test another 4.6 million SNPs from publicly available databases, and add that information to the map. As a result of a grant competition last summer, Perlegen received a $6.1 million award from the National Human Genome Research Institute (NHGRI), part of the National Institutes of Health (NIH), to add data on 2.25 million additional SNPs to HapMap. The new development, enabled by a partnership among multiple funding sources, will expand that effort and test virtually the entire known catalog of human variation on the HapMap samples. This will increase the density of SNP "signposts" across the genome from the current average of one every 3,000 bases to about one every 600 bases.

"This will help us create a far more powerful HapMap than we ever imagined. We sincerely thank all those who are giving their time, technology and money to help turn this dream into reality. The payoff will be a better understanding of the genetic risk factors underlying a wide range of diseases and conditions," said NHGRI Director Francis S. Collins, M.D., Ph.D.

The first phase of the HapMap Project has allowed scientists to make important analyses of the human genome that were not possible with just the human DNA sequence, and the International HapMap Consortium plans to publish its comprehensive analysis of this data later this year. The second phase of the project will provide researchers with a denser map that will enable them to more precisely narrow gene discovery to specific regions of the genome.

The effort to expand the HapMap is made possible by $3.3 million in additional support from a unique public-private partnership, including the following organizations: the Wellcome Trust, London, $624,000; Genome Canada/Genome Quebec, $260,000; Bristol-Myers Squibb Co., New York, $100,000; Pfizer Inc., New York, $100,000; Perlegen Sciences, at least $1.2 million (based on "in kind" services); and NHGRI, $1 million. The donations from the two pharmaceutical companies were coordinated by The SNP Consortium, Ltd., of Deerfield, Ill.

"Researchers are already using HapMap data to accelerate the search for genes involved in common diseases, as well as genes involved in drug responsiveness," said Karen Kennedy, Ph.D., science program manager at the Wellcome Trust. "When the more comprehensive version of the HapMap is completed this fall, such studies will be able to be carried out with even greater speed and efficiency."

To create the HapMap, DNA was taken from blood samples from volunteer donors from the following populations: Han Chinese in Beijing, Japanese in Tokyo, Yoruba in Ibadan, Nigeria and Utah residents with ancestry from northern and western Europe. No medical or personal
identifying information was obtained from the 270 donors. However, the samples are identified by the population from which they were collected.

Although any two people are 99.9 percent identical at the genetic level, understanding the one-tenth of one percent difference is important because it helps explain why one person may be more susceptible to a certain disease than another. For any given disease, such as type II diabetes or coronary artery disease, researchers can use the HapMap to compare the genetic variation patterns of a group of people known to have the disease with a group of people without the disease. Finding a certain pattern more often in people with the disease identifies a genomic region that may contain genes contributing to the condition. Because the Phase II HapMap will be so detailed, researchers will be able to use its SNP signposts to zero in on that particular genomic region and search for specific genes involved in that disorder. This approach can reduce the work and expense of searching the genome for hereditary factors in common disease by a factor of 20 to 40 compared with current, brute force approaches.

"This new partnership underscores the private sector’s enthusiasm for the HapMap and its potential as a tool for the understanding of disease. The willingness of these firms to contribute to building an even better map follows the collaborative tradition established by The SNP Consortium," said Arthur Holden, chairman and chief executive of The SNP Consortium.

In addition to affecting risk of disease, genetic variation has been shown to affect the response of people to therapeutic drugs, toxic substances and environmental factors, and the HapMap can assist in the identification of those variants. Since not all genetic variants are deleterious, the HapMap also may be used to help to pinpoint genetic variations that contribute to good health, such as those protecting against infectious diseases or promoting longevity.

"We are excited by the opportunity to apply our technology to all publicly available SNPs. This effort is so important that Perlegen is willing to contribute some of its own resources to make this possible," said Kelly A. Frazer, Ph.D., vice president of genomics at Perlegen. "We are confident that the end result of this public-private collaboration will be an outstanding human haplotype map that will provide a major new tool in the effort to combat human disease through an understanding of its genetic components."

Researchers around the globe can quickly access the HapMap data through free public databases, such as the HapMap Data Coordination Center (http://www.hapmap.org), the NIH-funded National Center for Biotechnology Information's dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/) and the JSNP Database in Japan (http://snp.ims.u-tokyo.ac.jp/).

"Adding this large number of new SNPs to the map will make it even easier for researchers to correlate genetic variation with gene function. Such information is crucial for the development of therapies and preventive strategies tailored to each person’s unique genetic makeup," said Martin Godbout, Ph.D., president and CEO of Genome Canada, who also was speaking on behalf of Genome Quebec.

The International HapMap Consortium is a public-private partnership of scientists and funding agencies from Canada, China, Japan, Nigeria, the United Kingdom and the United States. The U.S. component of the $135 million international project is led by NHGRI on behalf of the 19 institutes, centers and offices of the NIH that contributed funding. For more information on the International HapMap Project, see <http://genome.gov/10001688> or <http://www.hapmap.org/>. To see a complete list of participating research organizations, see <http://www.hapmap.org/groups.html>.
NEW NEURONS BORN IN ADULT RAT CORTEX  Recent evidence suggesting that antidepressants may act by triggering the birth of new neurons in the adult hippocampus,* the brain's memory hub, has heightened interest in such adult neurogenesis and raised the question: Could new neurons also be sprouting up in the parts of the adult brain involved in the thinking and mood disturbances of depression and anxiety?

Now, scientists at the National Institute of Health's (NIH) National Institute of Mental Health (NIMH) have found newly born neurons that communicate via the chemical messenger GABA (gamma-aminobutyric acid) in adult rat cortex, seat of higher order "executive" functions, and in the striatum, site of habits, reward and motor skill learning. In the cortex, the new neurons appear to arise from previously unknown precursor cells native to the area, rather than from cells migrating in from another area. NIMH's Drs. Heather Cameron, Alexandre Dayer, and colleagues, report on their findings in the January 31, 2005 "Journal of Cell Biology".

Their discovery adds to the scientific debate over adult neurogenesis, which has potential implications for understanding a variety of brain disorders, possibly including Alzheimer's and schizophrenia. While most researchers agree that new neurons are generated in the adult hippocampus and olfactory bulb, the existence of adult neurogenesis in other brain regions remains controversial.

The NIMH team used many more markers than previous studies to track newborn neurons as they matured and to identify the type of neurotransmitters they secreted. The markers exploited antibody affinities for specific proteins to tag particular cell types with telltale color codes, visible on brain slices under fluorescence with a laser-powered microscope.

The researchers found that the cortex and striatum were giving birth to new, widely scattered small cells, called interneurons, that make and secrete GABA, a neurotransmitter that dampens neuronal activity. The new interneurons closely resembled those seen in the hippocampus and olfactory bulb and seemed to arise at similar rates. Interneurons are thought to play a role in regulating larger types of neurons that make long-distance connections between brain regions and predominate in these areas.

The NIMH team was surprised to find that the new cortex interneurons appeared to arise from a previously unknown class of local precursor cells rather than from cells that migrate into the area from the subventricular zone, where other neurons - including those seen in the striatum and olfactory bulb - originate during adulthood. However, during development, both the cortex and striatum precursors likely stem from common ancestor cells that somehow retain their ability to divide and generate new GABA interneurons, propose the researchers.

"Since antidepressants increase neurogenesis in the adult hippocampus, they might have similar effects in the cortex, the region probably responsible for mood dysregulation in depression," suggested Cameron. "But answers to such questions about regulation and possible functions of the new neurons must await results of future studies."

Also participating the project were Kathryn Cleaver and Thamara Abouantoun of the NIMH Unit on Neuroplasticity. Dr. Dayer's work was supported by the Swiss National Fund.
NIMH is part of the National Institutes of Health (NIH), the Federal Government's primary agency for biomedical and behavioral research. NIH is a component of the U.S. Department of Health and Human Services.

An image of a newborn GABA neuron in adult rat neocortex can be found at: http://www.nimh.nih.gov/press/prcortexneurogenesis.cfm

NEW INHERITED DISEASE CAN CAUSE EARLY AORTIC RUPTURE HHMI researcher, Harry C. Dietz, M.D., The Johns Hopkins University School of Medicine, has identified a new inherited syndrome that can cause the heart's aorta to rupture earlier than other aortic aneurysm syndromes, such as Marfan syndrome. They said the newly identified syndrome is a relatively common disorder, which can be corrected with surgery if it is diagnosed early. This research was published in the January 30, 2005, issue of Nature Genetics. For the full story, go to http://www.hhmi.org/news/dietz2.html

INITIATIVE FOR ANNOTATING GENOMES PROPOSED A new report released by the American Academy of Microbiology recommends that a centralized genome annotation initiative be established in the U.S. that could lead to new applications in healthcare, biodefense, energy, the environment, and agriculture. Full Article

Notice of Comprehensive Identification of Tumor Mutations: Request for Information (NOT-CA-05-010) NIH is seeking input from the community on a project with an ultimate goal of large-scale identification of somatic mutations in cancer through the comparison of sequences of multiple tumor samples to reference sequence from normal tissue from the same individuals. The hypothesis is that the identification of somatic mutations will accelerate the development and application of diagnostic and therapeutic approaches for the prevention, diagnosis, and treatment of cancer.

This Request for Information (RFI) is for analysis and planning purposes only and should not be construed as a solicitation or as an obligation on the part of the Government. The Government does not intend to award a cooperative agreement, contract, or grant on the basis of responses to this RFI or otherwise pay for the preparation of any information submitted or for the Government's use of such information. http://grants.nih.gov/grants/guide/notice-files/NOT-CA-05-010.html

NIH CALLS ON SCIENTISTS TO SPEED PUBLIC RELEASE OF RESEARCH PUBLICATIONS: Online Archive Will Make Articles Accessible to the Public

The National Institutes of Health (NIH) announced today a new policy designed to accelerate the public's access to published articles resulting from NIH-funded research. The policy - the first of its kind for NIH - calls on scientists to release to the public manuscripts from research supported by NIH as soon as possible, and within 12 months of final publication.

These peer-reviewed, NIH-funded research publications will be available in a Web-based archive to be managed by the National Library of Medicine (NLM), a component of NIH. The online archive will increase the public's access to health-related publications at a time when demand for such information is on a steady rise.
"With the rapid growth in the public's use of the Internet, NIH must take a leadership role in making available to the public the research that we support," said NIH Director Elias A. Zerhouni, M.D. "While this new policy is voluntary, we are strongly encouraging all NIH-supported researchers to release their published manuscripts as soon as possible for the benefit of the public. Scientists have a right to see the results of their work disseminated as quickly and broadly as possible, and NIH is committed to helping our scientists exercise this right. We urge publishers to work closely with authors in implementing this policy."

"In developing this policy, we made a concerted effort to balance the importance of this archive to NIH's public health mission, with the need to provide flexibility for authors, their institutions, and publishers in those cases where immediate release is not possible," Zerhouni added. "NIH recognizes the importance of preserving quality peer review and the viability of a diversity of publishing models. Nevertheless, we expect that only in limited cases will authors deem it necessary to select the longest delay period."

The NIH policy will achieve several important goals, including:

(1) creating a stable archive of peer-reviewed research publications resulting from NIH-funded studies to ensure the permanent preservation of these vital research findings;

(2) securing a searchable compendium of these research publications that NIH and its awardees can use to manage more efficiently and to understand better their research portfolios, monitor scientific productivity, and, ultimately, help set research priorities; and

(3) making published results of NIH-funded research more readily accessible to the public, health care providers, educators, and scientists.

Beginning May 2, 2005, the policy requests that NIH-funded scientists submit an electronic version of the author's final manuscript, upon acceptance for publication, resulting from research supported in whole or in part by NIH. The author's final manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process.

The policy gives authors the flexibility to designate a specific time frame for public release ranging from immediate public access after final publication to a 12 month delay - when they submit their manuscripts to NIH. Authors are strongly encouraged to exercise their right to specify that their articles will be publicly available through PubMed Central (PMC) as soon as possible.

PMC ([http://www.pubmedcentral.nih.gov](http://www.pubmedcentral.nih.gov)), a part of the NIH's National Library of Medicine (NLM), is the agency's digital repository of full-text, peer-reviewed biomedical, behavioral, and clinical research journals. It is a publicly-accessible, stable, permanent, and searchable electronic archive.

The release of this policy follows months of intensive deliberations with representatives of patient and scientific organizations, researchers, and publishers. NIH posted the draft policy for public comment in September, and received and reviewed over 6,000 public comments.

As part of on-going efforts to implement this new policy, NIH plans to establish a Public Access Advisory Working Group, as a subgroup of the NLM's Board of Regents. The Working Group will include representatives of the patient advocacy, scientific, library, and publishing communities, and will provide advice on implementation issues and assess progress in meeting the new policy's stated goals.
Additional information on the new policy and related documents, including a "Questions and Answers" fact sheet, can be found at: <http://www.nih.gov/about/publicaccess/index.htm>.

The NIH comprises the Office of the Director and 27 Institutes and Centers. The Office of the Director is the central office at NIH, and is responsible for setting policy for NIH and for planning, managing, and coordinating the programs and activities of all the NIH components. The NIH, the Nation's medical research agency, is a component of the U.S. Department of Health and Human Services. It is the primary Federal agency for conducting and supporting basic, clinical, and translational medical research, and investigates the causes, treatments, and cures for both common and rare diseases. For more information, visit <http://www.nih.gov>.

**HOW MANY COMPARATIVE GENOMES ARE ENOUGH?**

As the human genome sequence neared completion several years ago, geneticists eagerly began discussing which other organisms to sequence -- partly to see which DNA regions are similar across species and therefore likely to serve critical functions. But these discussions raised an important, and potentially expensive, question: How many species need to be sequenced to know whether evolution has conserved a given stretch of DNA?

Now, HHMI researchers, led by Sean R. Eddy, Ph.D. from Washington University School of Medicine, have developed a mathematical model that answers this question. "We shouldn't make these decisions based on seat-of-the-pants intuitions," said HHMI investigator Sean Eddy. "It's important to lay out the case that these genomes really do have tremendous value for analyzing the human genome sequence."


**THE SHAPES OF LIFE: NIGMS PROJECT YIELDS MORE THAN 1,000 PROTEIN STRUCTURES**

The Protein Structure Initiative (PSI), a national program aimed at determining the three-dimensional shapes of a wide range of proteins, has now determined more than 1,000 different structures. These structures will shed light on how proteins function in many life processes and could lead to targets for the development of new medicines.

The PSI is a 10-year, approximately $600 million project funded largely by the National Institute of General Medical Sciences (NIGMS), part of the National Institutes of Health. The first half of this project - a pilot phase that started in 2000 - has centered on developing new tools and processes that enable researchers to quickly, cheaply, and reliably determine the shapes of many proteins found in nature.

"One thousand protein structures is a significant milestone for the PSI, and it shows an impressive return on the investment in the technology and methods for rapid structure determination," said Jeremy M. Berg, Ph.D., director of NIGMS. "These structures are interesting in their own right and provide the basis for modeling many important proteins."

Some of the newly determined structures are of proteins found in plants, mice, yeast, and bacteria, including the pathogenic types that cause pneumonia, anthrax, and tuberculosis.

The nine PSI pilot centers have transformed protein structure determination from a mostly manual process to a highly automated one. Robotic instruments rapidly clone, express, purify, crystallize, and analyze many proteins simultaneously, cutting the time it takes to determine a
single protein structure from months to days. For example, a robotic arm drops protein solution into thousands of tiny wells for crystallization trials, and an imaging system quickly scans the wells looking for signs of crystal formation - key to capturing protein structures.

"At this large scale, it would be unthinkable to do all these steps by hand," said John Norvell, Ph.D., director of the PSI at NIGMS and a scientist trained in protein structure determination. He noted that some robotics and automated tools have been refined and are now marketed by companies for general structural biology applications.

As the PSI pilot centers have put automated structure determination pipelines in place, the number of protein structures they have solved has increased significantly. In the second, third, and fourth years of the pilot phase, the centers in aggregate reported 109, 217, and 348 structures, respectively. Now, halfway through the fifth year, they've surpassed a total of 1,000. Many of these structures are very different from previously known structures, said Norvell.

The findings contribute to the initiative's ultimate goal of providing structural information on 4,000-6,000 unique proteins that represent the variety found in organisms ranging from bacteria to humans. Researchers can use these structures, which are determined experimentally, to build computer models of the structures of other proteins with related amino acid sequences.

Although the main focus of the second phase of the PSI will be on solving protein structures, Norvell said there will be continued development of new technology: "As we reach for higher-hanging fruit - protein structures that are more complex and harder to solve - we will need to develop additional tools and methods."

As part of the PSI effort, all the structures determined by the centers are collected, stored, and made publicly available by the Protein Data Bank (PDB), <http://www.rcsb.org/pdb/>, a repository of three-dimensional biological structure data.

"The protein structures solved by the PSI are more than a scientific stamp collection," explained Norvell. "They will help researchers better understand the function of proteins, predict the shape of unknown proteins, quickly identify targets for drug development, and compare protein structures from normal and diseased tissues." In general, a broad range of biomedical researchers will benefit from the PSI's technical advances, experimental data, and availability of new materials, such as reagents.

"There are a lot of proteins that are incredibly important to understanding human biology and medicine, yet we know very little about most of them," said Norvell. "The PSI will provide important information about these molecules so vital to life."

The nine pilot centers participating in the first phase of the PSI are:

-- The Berkeley Structural Genomics Center, <http://www.strgen.org/>
-- The Joint Center for Structural Genomics, <http://www.jcsq.org/>
-- The Southeast Collaboratory for Structural Genomics, http://www.secsg.org/


The pilot phase of the PSI will end in mid-2005. Centers for the second phase will be announced in July 2005.

In addition to NIGMS, the PSI currently receives funding from the National Institute of Allergy and Infectious Diseases, a component of the National Institutes of Health.

For more information about the PSI, please visit <http://www.nigms.nih.gov/psi/>. To schedule an interview with Jeremy M. Berg, Ph.D., or John Norvell, Ph.D., please contact the NIGMS Office of Communications and Public Liaison at 301-496-7301.

NIGMS is one of the 27 components of NIH, the premier federal agency for biomedical research. The NIGMS mission is to support basic biomedical research that lays the foundation for advances in disease diagnosis, treatment and prevention.

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This NIH News Release is available online at:

**TSC INFORMATION**

For information about TSC, visit the TS Alliance Web site at: http://www.tsalliance.org or call the Tuberous Sclerosis Alliance at 1-800-225-6872.