



TSC ALERT

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June/July 2004

Welcome to the June/July 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 August 2004 *TSC Alert* contact: Vicky.Whittemore@tsalliance.org

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IMPORTANT DEADLINES:

August 1, 2004: Submission of poster abstracts for late breaking research will be accepted until August 1st 2004.

'TSC genes - function and dysfunction - from molecular biology to therapeutic advances'

September 16-18, 2004

Queens' College
University of Cambridge
Cambridge, UK

Chairmen: Professor Patrick Bolton & Dr John Yates
Sponsored by the Tuberous Sclerosis Association

Pivotal roles for the TSC genes in cell biology have come from new research since 2001. In turn, this knowledge has increased understanding of the clinical manifestations of Tuberous Sclerosis. The 2004 conference will present new research around two main themes 'Normal function of TSC genes' and 'Clinical dysfunction caused by TSC gene mutations'. There will be plenary sessions on each theme, poster presentations and an opportunity to talk about any late breaking research.

For more information, visit the Tuberous Sclerosis Association Web site: <http://www.tuberous-sclerosis.org/research/conference/index.shtml>

GRANT ANNOUNCEMENTS:

TS ALLIANCE ANNOUNCES GRANT AWARDS FOR FY05

The Tuberous Sclerosis Alliance has approved funding for the following grants for FY2005:

- **Planning Grant for TSC Multicenter Clinical Trials**
Sandy Dabora, M.D., Ph.D.; Brigham and Women's Hospital, Boston, MA
7/1/04-6/30/05 - \$50,000
- **Regulation of TOR by TSC Signaling in Drosophila**
Thomas Neufeld, Ph.D., University of Minnesota, Minneapolis, MN
7/1/04-6/30/05 - \$146,893
- **Preclinical Evaluation of Alternative Therapeutic Targets**
Fellow: Xiuyun Jiang, Ph.D.; University of Washington, Seattle, WA
Sponsor: Ray Yeung, M.D.
7/1/04- 6/30/07 - \$150,000
- **Conference Grant: Pathophysiology of Epilepsy in Tuberous Sclerosis**
Gregory Holmes, M.D.; Dartmouth-Hitchcock Medical Center, NH
7/1/04- 12/31/04 - \$42,320
- **Mechanisms of Epileptogenesis in TSC**
Fellow: Delia Talos, M.D.; Children's Hospital, Boston, MA
Sponsor: Frances Jensen, M.D.
7/1/04- 6/30/07 - \$150,000

WOMEN IN NEUROSCIENCE TRAVEL AWARDS

DEADLINE EXTENSION: New due date for all applications is July 18, 2004

Women in Neuroscience (WIN) seeks to promote the careers of women neuroscientists around the world. All female and male undergraduate, graduate, and postdoctoral students who will be presenting as first author at Neuroscience 2004 are eligible for the Eli Lilly and WIN Pfizer Travel Award. Applications are due by July 18, 2004. Complete instructions and application forms are available on the WIN Web site. For more information, please contact awards co-chair Mel Dickerson melvin.dickerson@pfizer.com. Seeking reviewers: WIN is seeking men and women with at least three years of postdoctoral experience to review travel award applications. If you would like to volunteer as a reviewer, please contact awards co-chair Jen McCormick at jenmac@umich.edu. For more information: <http://www.womeninneuroscience.org>

ANNOUNCING THE HIGH PRIORITY, SHORT-TERM PROJECT AWARD (R56) (NOT-OD-04-047)

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-047.html>

SBIR/STTR: CIRCULATING CELLS AND DNA IN CANCER DETECTION (RFA-CA-06-001)

National Cancer Institute

APPLICATION RECEIPT DATES: February 14, 2005; June 13, 2005; October 12, 2005

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

ENVIRONMENTAL JUSTICE: PARTNERSHIPS FOR COMMUNICATION (RFA-ES-04-007)

Centers for Disease Control and Prevention

National Institute of Environmental Health Sciences

National Institute for Occupational Safety and Health

APPLICATION RECEIPT DATE: November 17, 2004

<http://grants.nih.gov/grants/guide/rfa-files/RFA-ES-04-007.html>

WOMEN'S REPRODUCTIVE HEALTH RESEARCH CAREER DEVELOPMENT PROGRAM

(RFA-HD-04-014)

National Institute of Child Health and Human Development

Office of Research on Women's Health

APPLICATION RECEIPT DATE: August 27, 2004

<http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-04-014.html>

STATE IMPLEMENTATION OF EVIDENCE-BASED PRACTICES II - BRIDGING SCIENCE AND SERVICE (RFA-MH-05-004)

Substance Abuse and Mental Health Services Administration

National Institute of Mental Health

Center for Mental Health Services

APPLICATION RECEIPT DATE: October 14, 2004

<http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-05-004.html>

MIDCAREER INVESTIGATOR AWARD IN PATIENT-ORIENTED RESEARCH (K24)(PA-04-107)

National Institute on Aging

National Institute on Alcohol Abuse and Alcoholism

National Institute of Allergy and Infectious Diseases

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Biomedical Imaging and Bioengineering

National Cancer Institute

National Institute of Child Health and Human Development

National Institute on Deafness and Other Communication Disorders

National Institute of Dental and Craniofacial Research

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute on Drug Abuse

National Institute of Environmental Health Sciences

National Institute of Nursing Research

National Eye Institute

National Heart, Lung, and Blood Institute

National Institute of Mental Health
National Institute of Neurological Disorders and Stroke
National Center for Complementary and Alternative Medicine
National Center for Research Resources
APPLICATION RECEIPT DATE(S): Multiple dates, see announcement
<http://grants.nih.gov/grants/guide/pa-files/PA-04-107.html>

REQUEST FOR INFORMATION: DESIGN AND IMPLEMENTATION OF A LARGE-SCALE PROSPECTIVE COHORT STUDY OF GENETIC AND ENVIRONMENTAL INFLUENCES ON COMMON DISEASES (NOT-OD-04-046)

National Institutes of Health
<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-046.html>

INTELLECTUAL PROPERTY RIGHTS IN GENETICS AND GENOMICS (RFA-HG-04-004)

National Human Genome Research Institute
APPLICATION RECEIPT DATE: November 18, 2004
<http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-04-004.html>

mRNA PROFILING OF THE MAJOR MENTAL DISORDERS: EXPLOITING POSTMORTEM HUMAN TISSUE THROUGH GENE ARRAY TECHNOLOGY (RFA-MH-05-005)

National Institute of Mental Health
APPLICATION RECEIPT DATE: August 17, 2004
<http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-05-005.html>

CENTERS FOR POLYCYSTIC KIDNEY DISEASE RESEARCH (RFA-DK-04-011)

National Institute of Diabetes and Digestive and Kidney Diseases
APPLICATION RECEIPT DATE: March 15, 2005
<http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-04-011.html>

PKD RESEARCH AND TRANSLATION CORE CENTERS (RFA-DK-04-012)

National Institute of Diabetes and Digestive and Kidney Diseases
APPLICATION RECEIPT DATE: March 15, 2005
<http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-04-012.html>

DATA COORDINATING CENTER FOR NATIONAL COLLABORATIVE PEDIATRIC CRITICAL CARE RESEARCH NETWORK (RFA-HD-04-015)

National Institute of Child Health and Human Development
APPLICATION RECEIPT DATE: August 9, 2004
<http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-04-015.html>

RESEARCH ON PSYCHOPATHOLOGY IN INTELLECTUAL DISABILITIES (MENTAL RETARDATION) (PA-04-044)

<http://grants2.nih.gov/grants/guide/pa-files/PA-04-044.html>

THE FETAL BASIS OF ADULT DISEASE: ROLE OF THE ENVIRONMENT (PAR-04-104)

National Institute of Environmental Health Sciences
APPLICATION RECEIPT DATE: August 12, 2004

<http://grants.nih.gov/grants/guide/pa-files/PA-04-104.html>

NOVEL APPROACHES TO ENHANCE ANIMAL STEM CELL RESEARCH (PA-04-125)

National Center for Research Resources
National Cancer Institute
National Eye Institute
National Heart, Lung and Blood Institute
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Biomedical Imaging and Bioengineering
National Institute of Child Health and Human Development
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Environmental Health Sciences
National Institute of Mental Health
National Institute of Neurological Disorders and Stroke
National Institute on Aging
National Institute on Deafness and Other Communication Disorders
National Institute on Drug Abuse

APPLICATION RECEIPT DATE(S): Multiple dates, see announcement

<http://grants.nih.gov/grants/guide/pa-files/PA-04-125.html>

SUPPLEMENTS TO PROMOTE REENTRY INTO BIOMEDICAL AND BEHAVIORAL RESEARCH CAREERS (PA-04-126)

National Institute on Aging
National Institute on Alcohol Abuse and Alcoholism
National Institute of Allergy and Infectious Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Biomedical Imaging and Bioengineering
National Cancer Institute
National Institute of Child Health and Human Development
National Institute on Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute on Drug Abuse
National Institute of Environmental Health Sciences
National Eye Institute
National Institute of General Medical Sciences
National Heart, Lung, and Blood Institute
National Human Genome Research Institute
National Institute of Mental Health
National Institute of Neurological Disorders and Stroke
National Institute of Nursing Research
National Center for Complementary and Alternative Medicine
National Center for Research Resources
Fogarty International Center
Office of Dietary Supplements
Office of Research on Women's Health

APPLICATION RECEIPT DATE(S): Contact participating NIH Institutes and Centers

<http://grants.nih.gov/grants/guide/pa-files/PA-04-126.html>

HIGH-ACCURACY PROTEIN STRUCTURE MODELING (RFA-GM-05-008)

National Institute of General Medical Sciences
APPLICATION RECEIPT DATE: February 14, 2005
<http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-05-008.html>

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.



AMERICAN SKIN ASSOCIATION

Deadline: October 4, 2004

Through its national grants and awards program, the ASA has given more than \$3.5 million in recognition and support of research to promising physician/scientists and leading figures in the field, and to research centers at major institutions throughout the country. Its grants program includes:

- \$50,000 Research Scholar Awards
- \$15,000 Research Grants
- \$15,000 Grants for Health Services/Quality of Life/Outcome Studies
- \$7,000 Medical Student Stipends
- Achievement Awards
- Lifetime Achievement Awards

Their website is <http://www.americanskin.org/frameset.htm>

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 or Vicky.whittemore@tsalliance.org

RESOURCES:

Tsc1 MICE NOW AVAILABLE

B6;129S4-Tsc1<tm1.1Djk>, is now being distributed from the NCI-Frederick MMHCC Repository. Breeder pairs are available from the Repository and data sheets and ordering information are available from their website: <http://web.ncifcrf.gov/researchresources/mmhcc/>

ALL KINDS OF MINDS

All Kinds of Minds, founded by Mel Levine, M.D., is a non-profit institute for the understanding of differences in learning. Excellent resources are provided for families, educators and clinicians. For more information, visit the Web site at: <http://www.allkindsofminds.org>

NEW TSC PUBLICATIONS:

TSC BASIC SCIENCE HIGHLIGHT:

Uhlmann EJ, Li W, Scheidenhelm DK, Gau CL, Tamanoi F, Gutmann DH (2004) **Loss of tuberous sclerosis complex 1 (Tsc1) expression results in increased Rheb/S6K pathway signaling important for astrocyte cell size regulation.** *Glia* 47(2):180-8

Individuals with tuberous sclerosis complex (TSC) develop central nervous system abnormalities that may reflect astrocyte dysfunction. In an effort to model astrocyte dysfunction in TSC, Uhlmann and colleagues at Washington University, St. Louis, MO, generated mice lacking Tsc1 (hamartin) expression in astrocytes and demonstrated that Tsc1-null astrocytes exhibit abnormalities in contact inhibition growth arrest. In this study, they demonstrate that hamartin-deficient astrocytes are also defective in cell size regulation. They show that the increase in Tsc1-null astrocyte size is associated with increased activation of the S6-kinase pathway. In keeping with recent reports that the hamartin/tuberin complex may regulate Rheb and downstream S6K activation, they demonstrate that expression of either Rheb or S6K in primary astrocytes results in increased S6 pathway activation, and that inhibition of Rheb activity in Tsc1-deficient astrocytes using either pharmacologic or genetic strategies markedly reduces S6 activation. Collectively, these observations suggest that TSC inactivation in astrocytes results in defective cell size regulation associated with dysregulated Rheb/mTOR/S6K pathway activity.

TSC CLINICAL SCIENCE HIGHLIGHT

Mackay MT, Weiss SK, Adams-Webber T, Ashwal S, Stephens D, Ballaban-Gill K, Baram TZ, Duchowny M, Hirtz D, Pellock JM, Shields WD, Shinnar S, Wyllie E, Snead OC 3rd; American Academy of Neurology; Child Neurology Society (2004) **Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society.** *Neurology* 62(10):1668-81
<http://www.neurology.org/cgi/content/full/62/10/1668>

OBJECTIVE: To determine the current best practice for treatment of infantile spasms in children.
METHODS: Database searches of MEDLINE from 1966 and EMBASE from 1980 and searches of reference lists of retrieved articles were performed. Inclusion criteria were the documented presence of infantile spasms and hypsarrhythmia. Outcome measures included complete

cessation of spasms, resolution of hypsarrhythmia, relapse rate, developmental outcome, and presence or absence of epilepsy or an epileptiform EEG. One hundred fifty-nine articles were selected for detailed review. Recommendations were based on a four-tiered classification scheme. RESULTS: Adrenocorticotrophic hormone (ACTH) is probably effective for the short-term treatment of infantile spasms, but there is insufficient evidence to recommend the optimum dosage and duration of treatment. There is insufficient evidence to determine whether oral corticosteroids are effective. Vigabatrin is possibly effective for the short-term treatment of infantile spasm and is possibly also effective for children with tuberous sclerosis. Concerns about retinal toxicity suggest that serial ophthalmologic screening is required in patients on vigabatrin; however, the data are insufficient to make recommendations regarding the frequency or type of screening. There is insufficient evidence to recommend any other treatment of infantile spasms. There is insufficient evidence to conclude that successful treatment of infantile spasms improves the long-term prognosis. CONCLUSIONS: ACTH is probably an effective agent in the short-term treatment of infantile spasms. Vigabatrin is possibly effective.

TSC PUBLICATIONS:

Adhvaryu K, Shanbag P, Vaidya M (2004) Tuberous sclerosis with hypothyroidism and precocious puberty. *Indian J Pediatr* 71(3):273-5

<http://www.ijppediatricsindia.org/article.asp?issn=0019-5456;year=2004;volume=71;issue=3;spage=273;epage=275;aulast=Adhvaryu>

Alam H, Maizels ET, Park Y, Ghaey S, Feiger ZJ, Chandel NS, Hunzicker-Dunn M (2004) Follicle-stimulating hormone activation of hypoxia-inducible factor-1 by the phosphatidylinositol 3-kinase/AKT/Ras homolog enriched in brain (Rheb)/mammalian target of rapamycin (mTOR) pathway is necessary for induction of select protein markers of follicular differentiation. *J Biol Chem* 279(19):19431-40; Epub 2004 Feb 24

Alfonso I, Vasconcellos E, Shuhaiber HH, Yaylali I, Papazian O (2004) Bilateral decreased oxygenation during focal status epilepticus in a neonate with hemimegalencephaly. *J Child Neurol* 19(5):394-6

Asato MR, Hardan AY (2004) Neuropsychiatric problems in tuberous sclerosis complex. *J Child Neurol* 19(4):241-9

Aspuria PJ, Tamanoi F (2004) The Rheb family of GTP-binding proteins. *Cell Signal* 16(10):1105-12

Birchenall-Roberts MC, Fu T, Bang OS, Dambach M, Resau JH, Sadowski CL, Bertolotto DC, Lee HJ, Kim SJ, Ruscetti FW (2004) Tuberous Sclerosis Complex 2 Gene Product Interacts with Human SMAD Proteins: A Molecular Link of Two Tumor Suppressor Pathways. *J Biol Chem* 279(24):25605-13; Epub 2004 Apr 02

Browne GJ, Proud CG (2004) A novel mTOR-regulated phosphorylation site in elongation factor 2 kinase modulates the activity of the kinase and its binding to calmodulin. *Mol Cell Biol* 24(7):2986-97

Buoni S, Zannolli R, Strambi M, Fois A (2004) Combined treatment with vigabatrin and topiramate in West syndrome. *J Child Neurol* 19(5):385-6

Caprez C, Walling AD, Reimer CM (2004) Tuberous sclerosis complex in a young woman diagnosed incidentally on the basis of pregnancy ultrasonography. *South Med J* 97(5):512-5

Chetty R, Asa SL (2004) Pancreatic endocrine tumors: an update. *Adv Anat Pathol* 11(4):202-10

Cho NH, Shim HS, Choi YD, Kim DS (2004) Estrogen receptor is significantly associated with the epithelioid variants of renal angiomyolipoma: A clinicopathological and immunohistochemical study of 67 cases. *Pathol Int* 54(7):510-5

Cleary-Goldman J, Sanghvi AV, Nakhuda GS, Robinson JN (2004) Conservative management of pulmonary lymphangiomyomatosis and tuberous sclerosis complicated by renal angiomyolipomas in pregnancy. *J Matern Fetal Neonatal Med* 15(2):132-4

Corradetti MN, Inoki K, Bardeesy N, DePinho RA, Guan KL (2004) Regulation of the TSC pathway by LKB1: evidence of a molecular link between tuberous sclerosis complex and Peutz-Jeghers syndrome. *Genes Dev* 18(13):1533-8

Darling TN (2004) Hamartomas and tubers from defects in hamartin-tuberin. *J Am Acad Dermatol* 51(1 Pt 2):9-11

Daumke O, Weyand M, Chakrabarti PP, Vetter IR, Wittinghofer A (2004) The GTPase-activating protein Rap1GAP uses a catalytic asparagine. *Nature* 429(6988):197-201

Ekong R, Jeremiah S, Judah D, Lehmann O, Mirzayans F, Hung YC, Walter MA, Bhattacharya S, Gant TW, Povey S, Wolfe J (2004) Chromosomal anomalies on 6p25 in iris hypoplasia and Axenfeld-Rieger syndrome patients defined on a purpose-built genomic microarray. *Hum Mutat* 24(1):76-85

El-Hashemite N, Zhang H, Walker V, Hoffmeister KM, Kwiatkowski DJ (2004) Perturbed IFN-gamma-Jak-signal transducers and activators of transcription signaling in tuberous sclerosis mouse models: synergistic effects of rapamycin-IFN-gamma treatment. *Cancer Res* 64(10):3436-43

Fassunke J, Blumcke I, Lahl R, Elger CE, Schramm J, Merkelbach-Bruse S, Mathiak M, Wiestler OD, Becker AJ (2004) Analysis of chromosomal instability in focal cortical dysplasia of Taylor's balloon cell type. *Acta Neuropathol (Berl)* 108(2):129-34. Epub 2004 May 14

Fauser S, Becker A, Schulze-Bonhage A, Hildebrandt M, Tuxhorn I, Pannek HW, Lahl R, Schramm J, Blumcke I (2004) CD34-immunoreactive balloon cells in cortical malformations. *Acta Neuropathol (Berl)* 2004 Jun 19 [Epub ahead of print]

Fingar DC, Blenis J (2004) Target of rapamycin (TOR): an integrator of nutrient and growth factor signals and coordinator of cell growth and cell cycle progression. *Oncogene* 23(18):3151-71

Garaci FG, Floris R, Bozzao A, Manenti G, Simonetti A, Lupattelli T, Curatolo P, Simonetti G (2004) Increased Brain Apparent Diffusion Coefficient in Tuberous Sclerosis. *Radiology* 2004 Jun 23 [Epub ahead of print]

Guttridge DC (2004) Signaling pathways weigh in on decisions to make or break skeletal muscle. *Opin Clin Nutr Metab Care* 7(4):443-450

Hansen IA, Attardo GM, Park JH, Peng Q, Raikhel AS (2004) Target of rapamycin-mediated amino acid signaling in mosquito anautogeny. *Proc Natl Acad Sci U S A*. 2004 Jun 30 [Epub ahead of print]

- Hengstschlager M, Rosner M, Fountoulakis M, Oh JE, Lubec G (2004) Protein levels of alpha1-tubulin, protein disulfide isomerase, tropomyosins and vimentin are regulated by the tuberous sclerosis gene products. *Cancer Lett* 210(2):219-26
- Heywood G, Smyrk TC, Donohue JH (2004) Primary angiomyolipoma of the pancreas. *Pancreas* 28(4):443-5
- Jansen FE, van Nieuwenhuizen O, van Huffelen AC (2004) Tuberous sclerosis complex and its founders. *J Neurol Neurosurg Psychiatry* 75(5):770
- Jones KA, Jiang X, Yamamoto Y, Yeung RS (2004) Tuberin is a component of lipid rafts and mediates caveolin-1 localization: role of TSC2 in post-Golgi transport. *Exp Cell Res* 295(2):512-24
- Kapahi P, Zid BM, Harper T, Koslover D, Sapin V, Benzer S (2004) Regulation of Lifespan in *Drosophila* by Modulation of Genes in the TOR Signaling Pathway. *Curr Biol* 14(10):885-90
- Karbowniczek M, Cash T, Cheung M, Robertson GP, Astrinidis A, Henske EP (2004) Regulation of B-Raf kinase activity by tuberin and Rheb is mTOR independent. *J Biol Chem* 2004 May 18 [Epub ahead of print] <http://www.jbc.org/cgi/reprint/M402591200v1>
- Kauffmann E, Randrianaivo H, Boumahni B, Roman H, Laffitte A, Dumas H, Barau G, Fourmaintraux A (2004) [Post mortem brain MRI: an alternative for pathology examination in Bourneville tuberous sclerosis of the fetus?] *J Gynecol Obstet Biol Reprod (Paris)* 33(3):245-7 [Article in French]
- Kimball SR, Jefferson LS (2004) Molecular mechanisms through which amino acids mediate signaling through the mammalian target of rapamycin. *Curr Opin Clin Nutr Metab Care* 7(1):39-44
- Kolb TM, Davis MA (2004) The Tumor Promoter 12-O-Tetradecanoylphorbol 13-Acetate (TPA) Provokes a Prolonged Morphologic Response and ERK Activation in Tsc2-Null Renal Tumor Cells. *Toxicol Sci* 2004 Jun 3 [Epub ahead of print]
- Laass MW, Spiegel M, Jauch A, Hahn G, Rupprecht E, Vogelberg C, Bartsch O, Huebner A (2004) Tuberous sclerosis and polycystic kidney disease in a 3-month-old infant. *Pediatr Nephrol* 19(6):602-8; Epub 2004 Mar 09
- Lee-Jones L, Aligianis I, Davies PA, Puga A, Farndon PA, Stemmer-Rachamimov A, Ramesh V, Sampson JR (2004) Sacrococcygeal chordomas in patients with tuberous sclerosis complex show somatic loss of TSC1 or TSC2. *Genes Chromosomes Cancer* 41(1):80-5
- Lu Z, Hu X, Li Y, Zheng L, Zhou Y, Jiang H, Ning T, Basang Z, Zhang C, Ke Y (2004) Human papillomavirus 16 E6 oncoprotein interferes with insulin signaling pathway by binding to tuberin. *J Biol Chem* 2004 Jun 1 [Epub ahead of print] <http://www.jbc.org/cgi/reprint/M403385200v1>
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- Merrilees MJ, Hankin EJ, Black JL, Beaumont B (2004) Matrix proteoglycans and remodelling of interstitial lung tissue in lymphangiomyomatosis. *J Pathol* 203(2):653-60
- Nagashima Y, Inayama Y, Kato Y, Sakai N, Kanno H, Aoki I, Yao M (2004) Pathological and molecular biological aspects of the renal epithelial neoplasms, up-to-date. *Pathol Int* 54(6):377-86
- O'Callaghan FJ, Harris T, Joinson C, Bolton P, Noakes M, Presdee D, Renowden S, Shiell A, Martyn CN, Osborne JP (2004) The relation of infantile spasms, tubers, and intelligence in tuberous sclerosis complex. *Arch Dis Child* 89(6):530-3
- Pan D, Dong J, Zhang Y, Gao X (2004) Tuberous sclerosis complex: from *Drosophila* to human disease. *Trends Cell Biol* 14(2):78-85
- Peng SS, Lee WT, Wang YH, Huang KM (2004) Cerebral diffusion tensor images in children with tuberous sclerosis: a preliminary report. *Pediatr Radiol* 34(5):387-92; Epub 2004 Mar 17
- Rose VM (2004) Neurocutaneous syndromes. *MO Med* 101(2):112-6
- Sarnat HB, Flores-Sarnat L (2004) Integrative classification of morphology and molecular genetics in central nervous system malformations. *Am J Med Genet* 126A(4):386-92
- Shah OJ, Hunter T (2004) Critical role of T-loop and H-motif phosphorylation in the regulation of S6 kinase 1 by the tuberous sclerosis complex. *J Biol Chem* 279(20):20816-23; Epub 2004 Mar 01
- Sharma M, Ralte A, Arora R, Santosh V, Shankar SK, Sarkar C (2004) Subependymal giant cell astrocytoma: a clinicopathological study of 23 cases with special emphasis on proliferative markers and expression of p53 and retinoblastoma gene proteins. *Pathology* 36(2):139-44
- Smirniotopoulos JG (2004) Neuroimaging of phakomatoses: Sturge-Weber syndrome, tuberous sclerosis, von Hippel-Lindau syndrome. *Neuroimaging Clin N Am* 14(2):171-83
- Tehrani M, Vettriano IM, Chang CH (2004) Localized nodular hypertrophy mimicking rhabdomyoma in the fetal heart: prenatal sonographic and pathology findings. *Pediatr Dev Pathol* 7(2):192-7
- Uhlmann EJ, Li W, Scheidenhelm DK, Gau CL, Tamanoi F, Gutmann DH (2004) Loss of tuberous sclerosis complex 1 (*Tsc1*) expression results in increased Rheb/S6K pathway signaling important for astrocyte cell size regulation. *Glia* 47(2):180-8
- Walker M, Samii A, Bird T (2004) Coexistence of tuberous sclerosis and Friedreich ataxia. *J Neurol Sci* 221(1-2):91-3
- Wenzel HJ, Patel LS, Robbins CA, Emmi A, Yeung RS, Schwartzkroin PA (2004) Morphology of cerebral lesions in the Eker rat model of tuberous sclerosis. *Acta Neuropathol (Berl)*. 2004 Jun 5 [Epub ahead of print]

TSC-RELATED PUBLICATIONS:

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CONFERENCES:

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

July 22-23, 2004

The Singapore International Neuroscience Conference: Mechanisms, Models and Medicine

Singapore

The two-day conference will cover four main themes: epilepsy, pain and cognition; ion channel and receptor function; genetics and mechanisms of neurodegenerative diseases; and neural stem cells.

<http://www.sinc.com.sg/>

September 16-18, 2004

TSC International Research Conference 2004

TSC Genes - Function and Dysfunction - From Molecular Biology to Therapeutic Advances

Organized by the Tuberous Sclerosis Association of Great Britain
Queens' College, University of Cambridge, Cambridge UK

Deadline for Submission of Poster Abstracts for late breaking research will be accepted until August 1, 2004.

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

November 6-7, 2004

New England Regional TSC Conference

Holiday Inn, Boston Logan, Boston, MA

Sponsored and organized by the NE Community Alliance of the Tuberous Sclerosis Alliance

For more information, contact Jeffrey Hargreaves at Jeffrey.hargreaves@verizon.net

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, contact April Cooper at ACoope@ardenrealty.com

Save the date! May 4-5, 2006

TSC International Research Conference 2006

Berlin, Germany

More information coming soon!

NEWS:

DELIVERY SYSTEM FOR RNAi GENE THERAPY OPENS DOOR TO THE BRAIN (Reprinted from Genomics & Proteomics) The use of gene therapy in the treatment of brain cancer is hindered by drug delivery problems. Large molecules such as monoclonal antibodies and viral vectors cannot cross the blood-brain barrier. A featured article in the June 1 issue of Clinical Cancer Research [Pardridge et al., vol. 10, pp. 3667-3677 (2004)] now describes the successful delivery of a nonviral RNAi gene therapy to brain tumors in mice, resulting in a significant increase in survival times.

The study, overseen by William Pardridge, MD, of the University of California Los Angeles Medical School, was initiated from a drug delivery angle. "We're a drug delivery lab, not an RNAi lab," Pardridge says. "It seemed like none of the RNAi people could learn drug delivery, so we learned RNAi." Their team designed short hairpin RNAs (shRNAs) against endothelial growth factor receptor (EGFR) and encoded it in a DNA plasmid. The plasmid was then encapsulated in an anionic liposome conjugated with polyethylene glycol (PEG), thus restricting uptake by the reticuloendothelial system. In addition, 1 to 2% of the PEG strands were conjugated with one of two monoclonal antibodies.

These antibodies represented a two level "lock and key" system for getting past the blood-brain barrier (BBB) and the tumor cell membrane (which behaves much like the BBB). The first

antibody, which acts as a secret password for getting past the mouse BBB, was targeted to the mouse transferrin receptor (TfR). After the TfR admits the "trojan horse" liposome, it is targeted to the tumor cell by a human insulin receptor.

"The reason this work is significant," says Pardridge, "is that this area of science is not going to be converted into a therapeutic until the problems of drug delivery are solved."

In addition to mice, this technique has also been tested in rats and rhesus monkeys. Pardridge estimates that with funding, this method could be used in clinical trials in two years. A potential hurdle along the way would be eliminating ectopic expression of the gene in noncancer cells. Possible solutions include careful engineering of the DNA promoter and designing shRNAs that target only mutant forms of EGFR, which are frequently expressed by cancer cells.

EPILEPSY DRUGS CAUSE BONE LOSS Epilepsy drugs can increase the rate of bone loss in older women, according to a study published in the June 8 issue of *Neurology*, the scientific journal of the American Academy of Neurology. Women over age 65 who were taking drugs for epilepsy were losing bone mass at nearly twice the rate of women who were not taking epilepsy drugs.

"If this rate of bone loss is not addressed, the risk of hip fracture for these women will jump by 29 percent over five years," said study author Kristine Ensrud, MD, MPH, of the VA Medical Center in Minneapolis, Minn., and the University of Minnesota. "Older women taking epilepsy drugs should be screened for osteoporosis and counseled about the importance of getting enough calcium and taking vitamin D supplements."

The study involved 6,044 women at least 65 years old. The women's bone density in the heel bone was measured at the beginning of the study and again an average of 5.7 years later. At that time, the women's bone density in the hip bones was also measured. Then 4,202 of the women completed another hip bone density test an average of 4.4 years later.

Women who were taking epilepsy drugs had a 1.8 greater average rate of bone loss in the heel bone than women who were not taking epilepsy drugs, and a 1.7 greater average rate of loss at the hip. The results did not change when researchers adjusted for other risk factors, such as age, estrogen use, poor health status, inactivity, smoking and lower calcium intake.

Ensrud said the two types of bone were tested because some researchers have hypothesized that epilepsy drugs affect only one type of bone, which is prevalent in the hip bone, but makes up only a fraction of the heel bone. "This study shows that the drugs affect both types of bone," Ensrud said.

It's not clear why or how epilepsy drugs affect bone loss. "It's possible that the drugs damage the body's ability to metabolize vitamin D or absorb calcium," Ensrud said.

The researchers monitored the women's use of epilepsy drugs by asking them to bring all of their current medications to their study appointments. Women who were taking epilepsy drugs at each appointment were classified as continuous epilepsy drug users. Women who were taking epilepsy drugs at some but not all of the appointments were called partial users.

The study found that the more frequently these medications were used, the greater the risk of bone density loss. Women who were continuous users had the highest average rate of bone loss. Women who were partial users had higher rates of bone loss than did women who did not take epilepsy drugs at any point during the study. For the heel bone, the average rate of bone loss was 1.46 percent of bone mass per year for non-users, compared to 1.74 percent per year for partial users and 2.35 percent for continuous users. For the hip bone, the rates were .7 percent for non-users, .87 percent for partial users and 1.16 percent for continuous users.

Of the 6,044 women who completed the heel bone tests, 41 were continuous epilepsy drug users, 61 were partial users and 5,942 were non-users. Of the 4,202 women who completed the hip bone tests, 40 were continuous users, 68 were partial users and 4,094 were non-users.

Ensrud noted that epilepsy, like osteoporosis, becomes more common as people age. An estimated 1.5 percent of people 65 and older have epilepsy, which is about twice the rate of younger adults. She also noted that the number of prescriptions for epilepsy drugs for conditions other than epilepsy has nearly doubled since 1991.

More background on epilepsy drugs and bone density can be found in a corresponding "Patient Page" at <http://www.neurology.org> The study was supported by grants from the National Institutes of Health.

HELPFUL OR HARMFUL? MEDICINAL VALUE OF MARIJUANA REMAINS UNCLEAR

Despite limited evidence of effectiveness, many epilepsy and multiple sclerosis patients believe marijuana is an effective treatment and are actively using it, according to two Canadian studies published in the June 8 issue of *Neurology*, the scientific journal of the American Academy of Neurology.

Multiple sclerosis patients in Halifax, Nova Scotia, and epilepsy patients in Edmonton, Alberta, recently participated in a questionnaire and a telephone survey, respectively, regarding patterns, prevalence and perceived effects of marijuana use. Results of these surveys may raise more questions than they answer.

In the study of epilepsy patients from the University of Alberta Epilepsy Clinic, 136 subjects responded to the phone survey. Of these, nearly half had used marijuana in their lifetime; one in five had used marijuana in the past year; 20 (15 percent) had used in the past month; 18 (13 percent) used more than 48 days per year; and 11 (8 percent) used more than half the days of the year. Four patients were actually considered marijuana dependent. Odds of frequent marijuana use were eight times greater for patients with frequent seizures and 10 times greater for those who had had epilepsy for at least five years.

One possible explanation for the association of marijuana use with seizure frequency is that patients who experience more frequent seizures might be more likely to try alternative treatments.

"Studies suggest one-third of the general population use alternative health care on a yearly basis," notes study author Donald Gross, MD, FRCP, of Walter C. Mackenzie Health Sciences Centre at the University of Alberta, Edmonton. "Not surprisingly, patients tend to look to alternative therapies in situations where conventional medicine has been unsuccessful, in particular, for chronic medical conditions. The finding of increased marijuana use in epilepsy

patients with longer duration of disease and frequent seizures is consistent with the findings regarding other forms of non-conventional therapies."

Another possible explanation for the correlation between increased seizure frequency and more frequent marijuana use is that there is a causal relationship between marijuana use and seizures, i.e. marijuana use leads to increased seizure frequency.

In the study of multiple sclerosis patients from Halifax, 205 subjects completed a survey questionnaire. Of the 34 identified medical marijuana users, more than half perceived it as being a very effective treatment, and more than half also reported using it within the previous 24 hours. Nineteen patients reportedly used marijuana more than one time per week, with eight patients reporting more than one daily use.

"We have learned several things from these patients," concludes study author Mark Ware, MBBS, MRCP, of McGill University, Montreal, who co-authored the study with John Clark, MD, FRCPC, of Capital Health and the Dalhousie University Faculty of Medicine, Halifax. "Firstly, that pain and spasms are not the only reasons for use, and the effects of marijuana on mood, sleep and stress are important areas of therapeutic need and should be addressed in clinical trials. Secondly, there is a wide variance in doses used, ranging from single puffs to more than a gram at a time. Clinical trials will also need to include early dose-finding phases and allow for subject variability in dose adjustments. Thirdly, marijuana appears to be well-tolerated, though some subjects experienced intolerable side effects and deterioration of symptoms."

Access to marijuana also emerged as an important obstacle in the use of this drug for medical purposes.

Nearly one in four epilepsy patients and one in six multiple sclerosis patients believe that marijuana is an effective form of treatment for their disease symptoms, and many are currently using marijuana therapeutically. Carefully controlled clinical trials are recommended by both study teams to determine the efficacy of marijuana in the treatment of epilepsy and multiple sclerosis.

The study by Gross et al received support from the University of Alberta Hospital Foundation. The study by Ware et al received support from a Dalhousie University summer research student award, Canadian Institutes of Health Research and the Fonds de la Recherche en Santé du Quebec.

FIBROID TUMORS LACK CRUCIAL STRUCTURAL PROTEIN Fibroid tumors - the sometimes painful uterine growths affecting many American women - lack a key protein that plays a role in holding tissues together, according to a study by researchers from the Uniformed Services University of the Health Sciences (USUHS) and the National Institute of Child Health and Human Development of the National Institutes of Health.

"This finding is a major step in understanding the nature of fibroids and may prove useful in efforts to devise more effective treatments for them," said Duane Alexander, M.D., Director of the NICHD.

The study has been published on line at <http://www3.interscience.wiley.com/cgi-bin/jhome/38250> and will appear in the July 2004 issue of "Genes, Chromosomes and Cancer".

Specifically, the researchers discovered that fibroids have low levels of the protein dermatopontin. The protein is a key component of the extracellular matrix - the elastic meshwork of collagen and other proteins that keeps cells in place. Moreover, the researchers learned that another type of growth, keloids, also lack dermatopontin. Keloids are an overgrowth of thick scar tissue that can form on the skin after a cut or other wound heals. Both keloids and fibroids disproportionately affect African Americans.

Fibroids, also known as leiomyomas, are noncancerous growths that develop in the myometrium, the smooth muscle tissue of the uterus, explained William Catherino, M.D., Ph.D., of NICHD's Pediatric and Reproductive Endocrinology Branch.

Women with fibroids may experience painful menstrual periods, pain during sexual intercourse, infertility, urinary and fecal incontinence, and bowel obstruction, Dr. Catherino said. They are also more likely to go into labor prematurely and to experience a miscarriage.

Dr. Catherino added that it's difficult to know exactly how many women in the United States have fibroids, because in many cases fibroids do not cause symptoms, he said. Some studies using ultrasound have indicated that 70 to 80 percent of women may have the growths but do not experience any problems from them. About one out of every 2 to 4 women will have symptoms from fibroids at some point during their reproductive years. For women who experience severe symptoms, treatment often involves surgery. In one form of surgery, myomectomy, the fibroids are removed from the wall of the uterus. In many cases, the fibroids return after surgery or their removal results in the formation of painful scar tissue.

In other cases, the number of fibroids is so great that hysterectomy (removal of the uterus) must be performed. According to the Centers for Disease Control and Prevention, fibroids are the single greatest reason for hysterectomy, accounting for 27 percent of the 650,000-675,000 hysterectomies performed in the United States each year.

In the study, researchers used a technique known as microarray analysis to determine the activity levels of genes in fibroid tumors. They examined both fibroid tissue and normal uterine tissue from 11 women who underwent hysterectomy as a treatment for fibroid symptoms. They also examined samples of keloid tissue provided by another lab.

The researchers found that the fibroid tissue had lower levels of dermatopontin than did the normal uterine tissue. They also discovered that keloid tissue had low levels of dermatopontin. Both the fibroid tissue and the keloid tissue contained disorganized, unstructured strands of collagen, Dr. Catherino said. In normal tissues, collagen forms discrete strands.

Dr. Catherino and his colleagues suspect that fibroid tumors have a genetic basis. Moreover, the same genetic factors that may predispose African American women to develop fibroids may also play a role in African Americans' predisposition toward keloids. He and his coauthors wrote that African American women are 3.3 times more likely to develop fibroids than are Caucasian American women and 3 times more likely to develop keloids than are Caucasian American women.

Other evidence also points to a genetic basis for fibroids. Women whose mothers, sisters or daughters have fibroids are more likely to have fibroids themselves. Similarly, women with the genetic disorders Alport Syndrome and Reed Syndrome are more likely than other women to have fibroids.

Dr. Catherino hypothesizes that dermatopontin plays a role in preventing the muscle cells of the uterus - known as myometrial cells - from developing into another type of cell. Dermatopontin

appears to react with the integrin receptor on myometrial cells. Like a key fits into a lock, molecules interact with cell receptors to bring about changes in the cell. The integrin receptor and molecule appear to be important for influencing the type of cell that a cell will become.

Dr. Catherino suspects that a failure of dermatopontin to interact with the integrin receptor results in the cell losing its function as a myometrial cell and becoming more like a fibroblast - a type of skin cell that produces collagen. In fact, the individual cells in fibroids are referred to as myofibroblasts, because they have characteristics of both myometrial cells and fibroblasts.

Additional information about fibroids is available from the NICHD publication, Uterine Fibroids. This publication, along with other NICHD publications, is available on the NICHD Web site, <http://www.nichd.nih.gov> or from the NICHD Information Resource Center, 1-800-370-2943; e-mail NICHDInformationResourceCenter@mail.nih.gov

SOCIETY FOR NEUROSCIENCE LAUNCHES THE NEUROSCIENCE DATABASE GATEWAY

The SfN Neuroscience Database Gateway (NDG) is now online. A pilot project developed by the Brain Information Group (BIG), the gateway provides access to 76 neuroscience-related databases. BIG has evaluated the current status of neuroscience databases; and assessed future directions of neuroscience data management, data sharing, and database interoperability. Read and comment on the White Paper on NDG, try out the Gateway, and complete an online survey. (www.sfn.org/ndg).

GENES PROMOTING NERVE, OTHER CELL COMMUNICATIONS MAY HAVE COME FROM BACTERIA

Some of the genes that allow nerve cells and some other types of cells to send elaborate chemical messages to each other appear to have been transferred to animals or their immediate ancestors from bacteria eons ago, according to a study by researchers from the National Library of Medicine and the National Institute of Child Health and Human Development, both part of the National Institutes of Health.

Specifically, the genes contain the information needed to make enzymes, which, in turn are crucial for making the complex molecules that cells use to communicate with each other. These cell-signaling molecules play a role in learning, memory, mental alertness, sleep patterns, and allergic responses.

The study was published on the web at <http://www.sciencedirect.com/science/journal/01689525> and will appear in the July issue of "Trends in Genetics". Bacteria are single celled organisms. In plants and animals, DNA is contained in a membrane bound compartment called the nucleus. The DNA of bacteria is not contained within a nucleus.

For the study, the researchers conducted a comprehensive search of the National Library of Medicine's genetic databases. They identified a group of genes needed to make some enzymes involved in the manufacture of the chemical messengers that cells use to communicate. The genes are present in bacteria and in vertebrate animals, but with a few exceptions, not in plants, or other complex living organisms. The search was prompted by the group's earlier observation that the enzyme arylalkylamine N-acetyltransferase (AANAT) was present in animals, bacteria, and yeast, but in no other living organisms. AANAT is used to make melatonin, a hormone that regulates the body's cycles of sleeping and waking.

The researchers also identified genes for enzymes that are involved in the manufacture of the following chemical messengers:

- acetylcholine - involved in learning and memory, muscle contraction,
- dopamine - the absence of which results in Parkinson's disease,
- norepinephrine and epinephrine - involved in alertness, vascular tone,
- serotonin - involved in mood,
- glutamate - involved in alertness,
- nitric oxide - involved in many bodily functions, including blood pressure regulation,
- histamine - involved in the allergic response

The bacterial genes may have been transferred to the organisms that were the ancestors of animals more than a half billion years ago, explained another of the study's authors, David Klein, Ph.D., a melatonin researcher at the National Institute of Child Health and Human Development (NICHD).

It is not known how the genes were transferred, but Dr. Klein theorizes that one form of transfer took place during the reproductive cycle, with the genes having been incorporated into either sperm or egg cells or incorporated shortly after fertilization. It's possible that the transfer could also represent a form of infection where genetic material is transferred into these reproductive cells and thereby into the entire genome of the recipient.

Bacteria do transfer genes to other bacteria, by means of a circular DNA molecule known as a plasmid. However, Dr. Klein said, bacteria are not believed to be capable of passing plasmids to animal cells.

The study's authors offered an alternative explanation for the fact that some genes are present only in bacteria and animals. According to this explanation, all living organisms once possessed these genes as well, and most lost them. However, the authors wrote that it is unlikely that such a large group of living organisms could have lost so many genes.

An understanding of how the enzymes function in bacteria may provide insight into how they function in animals, Dr. Klein said. All the enzymes may be important to bacteria because they provide a detoxification function - they make chemical changes within the bacteria that eliminate potentially toxic substances. AANAT, he said, is present in both the pineal gland, located in the brain, and in the retina of human beings and other primates. In the pineal gland, AANAT plays a role in manufacturing melatonin. However, AANAT in the retina does not manufacture melatonin. Dr. Klein suspects that, in the retina, AANAT may have a role in neutralizing and eliminating toxic substances. He is currently investigating whether a disruption in AANAT function plays a role in the development of macular degeneration, a disease that impairs vision and that may result in blindness.

"NOISY" GENES CAN HAVE BIG IMPACT HHMI researchers have revealed how it might be possible for randomness in gene expression to lead to differences in cells -- or people, for that matter -- that are genetically identical. This research was published in the March 27, 2004, issue of Science by Erin K. O'Shea, Ph.D., University of California, San Francisco. For the full story, go to <http://www.hhmi.org/news/oshea.html>

NIH ANNOUNCEMENTS:

NIH ROADMAP In September 2003, NIH Director Elias Zerhouni, M.D., announced the official launch of the NIH Roadmap for Biomedical Research, an innovative approach designed to speed the movement of research discoveries from bench to bedside. The Roadmap supports three broad areas: 1) New Pathways to Discovery; 2) Research Teams of the Future, including interdisciplinary research, high-risk research, and public-private partnerships; and 3) Re-engineering the Clinical Research Enterprise. NIH has solicited applications for numerous Roadmap activities since the September 2003 launch. Additional information on NIH Roadmap initiatives and funding opportunities is available at <http://nihroadmap.nih.gov/>.

HUMAN SUBJECTS PROTECTIONS On May 12, 2004, U.S. Department of Health and Human Services' Secretary Tommy G. Thompson released new guidance for protecting research subjects from possible harm caused by financial conflicts of interest. The guidance document, Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection, is for institutional review boards, investigators, research institutions and other interested parties. It applies to all human subjects research conducted or supported by HHS agencies or regulated by the Food and Drug Administration. The Federal Register notice can be viewed at <http://ohrp.osophs.dhhs.gov/humansubjects/finreltn/finalguid.pdf> and the U.S. Department of Health and Human Service's press release is available at <http://www.hhs.gov/news/press/2004pres/20040512.html>.

MORE THAN ONE-THIRD OF U.S. ADULTS USE COMPLEMENTARY AND ALTERNATIVE MEDICINE, ACCORDING TO NEW GOVERNMENT SURVEY
<http://www.nih.gov/news/pr/may2004/nccam-27.htm>

NIH GRANT APPLICATIONS NUMBERS INCREASE

The Center for Scientific Review has released a report stating that the number of NIH grant applications continues to rise. In fiscal year 2003, NIH experienced a 24 percent increase in the number of applications that it received over the previous fiscal year.
<http://www.csr.nih.gov/prnotes/may052804.pdf>

NATIONAL NIH INITIATIVE AIMS TO REDUCE KIDNEY FAILURE AMONG AFRICAN AMERICANS

The National Kidney Disease Education Program (NKDEP) began its first national effort to call attention to the seriousness of kidney disease and the importance of testing those at high risk, particularly African Americans, a group hit especially hard.

Kidney disease has no warning signs in its early stages and many of those at high risk do not know it. But its impact is clear. Twenty million people have kidney disease. The number of people already on dialysis or with a kidney transplant because their kidneys failed has doubled each decade for the past two decades. Nearly half a million people now have kidney failure - a number expected to surpass 660,000 by 2010. In addition to the human toll, the annual cost of treating patients with kidney failure in the United States is more than \$20 billion.

The impact of kidney disease is disproportionate among African Americans. They are four times more likely than Caucasians to develop kidney failure. And while African Americans make up just

12 percent of the population, they account for 30 percent of people with kidney failure. A significant disparity is found among African American men ages 22 to 44, who are 20-times more likely to develop kidney failure from hypertension compared to their Caucasian counterparts. "It's critical that we get in front of this growing epidemic. People's lives don't have to be devastated by kidney failure," says Thomas Hostetter, M.D., director of NKDEP, which is an initiative of the National Institutes of Health (NIH). "We want people at high risk for kidney disease, particularly African Americans, to know they are at risk and that they can do something about it."

That's the aim of NKDEP's "You Have The Power To Prevent Kidney Disease" campaign. It stresses three key messages: 1) know if you are at risk, 2) have your kidneys tested if you are at risk, and 3) kidney failure can be slowed or prevented if kidney disease is detected early. For more information about kidney disease or the "You Have The Power To Prevent Kidney Disease" campaign, visit <http://www.nkdep.nih.gov> or call 1-866-4-KIDNEY

NIH LAUNCHES EXPANDED HEALTH INFORMATION WEB SITE Valuable online resource provides links to wider range of health information - highlights popular health topics, cutting-edge science and interactive features. The National Institutes of Health (NIH) is pleased to announce the launch of an expanded health information Web site, available on the World Wide Web at: <http://health.nih.gov> The expanded site now offers links to a wider range of NIH's valuable resources, features colorful images to highlight an intriguing range of useful features, and gives readers the chance to test their health knowledge. Visitors can still access the popular "A to Z" listing of health topics, browse topics by body location/systems, or use the main "Search" box. Favorite health databases, such as Clinical Trials, MEDLINEplus, and PubMed, remain one click away. The newly expanded NIH health information Web site has information geared for the whole family, including kids, teens, parents, and seniors. Educators, clinicians, and researchers will continue to find the site a valuable resource of tools and guidelines.

NEW TECHFORLTC.ORG WEB SITE OFFERS COMPREHENSIVE INFORMATION ON TECHNOLOGIES FOR HEALTH PROFESSIONALS IN LONG-TERM CARE SETTINGS

HHS Secretary Tommy G. Thompson today announced the launch of a comprehensive, searchable Web site that contains information on hundreds of technology products to improve quality of life and care in long-term care residential settings.

Technology for Long Term Care is the result of a research project initiative by HHS to address barriers to bringing new technologies into residential care settings. Polisher Research Institute and IDEAS, Inc. constructed this Web site, <http://www.TechForLTC.org> under contract with the Office of the Assistant Secretary for Planning and Evaluation at HHS. The Web site was created to provide ready access to information on technologies that can help provide higher quality care for the elderly and the disabled. It will be especially useful for professionals in nursing homes, assisted living facilities, board and care facilities, adult day care facilities, and continuing care retirement communities. Extensive input was received from long-term care service providers, researchers, and state and federal officials to maximize its use and benefits.

By exploring the site, professionals can learn about low tech and high tech options currently available in four areas -- fall detection and prevention, wander management, calling for assistance, and incontinence. The site also highlights key issues to consider, such as regulatory concerns and resident quality of life, before selecting a technology. Once they decide which technology will meet their needs, they can search the site's extensive database to find specific products. A "Questions for Vendors" feature provides useful questions to ask vendors and manufacturers about their products.

Product information includes names, descriptions and details, price (when available), date last updated, the care issue and the category the product belongs to, and manufacturer/distributor contact information. The database will be continually updated to include the latest technological developments. Other care issues are planned to be added to the site in the future. Access to the Web site is unrestricted and free. More information about the site is available at www.TechForLTC.org

IMAGING STUDY SHOWS BRAIN MATURING

<http://www.nimh.nih.gov/press/prbrainmaturing.cfm>

RESEARCH TO TEST TREATMENT OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

<http://www.nimh.nih.gov/press/prturns.cfm>

NIH LAUNCHES FIRST CENTER IN NATIONWIDE CHEMICAL GENOMICS NETWORK

Initiative Will Generate New Tools to Accelerate Study of Human Disease The National Institutes of Health (NIH) announced the establishment of the NIH Chemical Genomics Center - the first component of a nationwide network that will produce innovative chemical "tools" for use in biological research and drug development. In contrast to researchers in the pharmaceutical industry, many academic and government scientists currently do not have easy access to large libraries of organic chemical compounds. Such compounds, which scientists call "small molecules" because they are smaller than proteins, can be used as tools to modulate gene function and improve understanding of biological pathways involved in human health and disease. This area of research is often referred to as chemical genomics.

Established through the Molecular Libraries and Imaging working group of the recently announced NIH Roadmap for Medical Research, the NIH Chemical Genomics Center is based in the National Human Genome Research Institute's (NHGRI) Division of Intramural Research. It is the first component of an initiative that will result in a consortium of chemical genomics screening centers. In addition to NHGRI, the National Institute of Mental Health (NIMH) is providing leadership for this initiative, which, like all of the Roadmap initiatives, includes representation from numerous NIH institutes and centers.

Up to 10 pilot centers will be funded at academic institutions and other locations across the country in Fiscal Year (FY) 2005. "These chemical genomics centers will be coordinated to build a network in the academic research community for identifying a broad range of small molecules with promising properties for biological research," said NIMH Director Thomas R. Insel, M.D.

To support the network, NIH plans to establish a repository to acquire, maintain and distribute a collection of up to 1 million chemical compounds. As was the case for the Human Genome Project, data generated by the chemical genomics network will be deposited in a central database, called PubChem, which will be managed by the National Center for Biotechnology Information at the National Library of Medicine and will be freely available to the entire scientific community.

With an eye toward expanding the frontiers of genomic exploration, the NIH Chemical Genomics Center plans to screen more than 100,000 small-molecule compounds in multiple high-throughput assays within its first year of operation. "Screening on the scale we are planning is unprecedented outside of the pharmaceutical and biotechnology industries. For the first time, biologists in the public sector will be able to take full advantage of the tremendous power of small molecules to serve as probes to advance our understanding of biology," said Dr. Austin.

To help achieve its ambitious goals, the NIH Chemical Genomics Center has selected a suite of ultra-high throughput target and pathway screening technologies from Kalypsys, Inc. of San Diego. The Kalypsys agreement, valued at up to \$30 million over the course of a four-year contract if all options are exercised, will deliver to the NIH center a suite of technologies, materials and services, including a highly automated robotic system capable of screening more than 1 million compounds per day in a variety of biochemical and cellular assays. Data gleaned from the screening effort will shed new light on the function of various genes and the roles that specific genes play in pathways crucial to biological function. Ultimately, researchers hope the information generated by the chemical genomics network will identify new targets for therapy and tools to study them, thereby enabling such targets to move more rapidly through the drug development pipeline.

RENAL PHYSICIANS AND NIH RELEASE WEB TOOL TO COORDINATE CARE FOR KIDNEY PATIENTS The Renal Physicians Association (RPA) and the National Kidney Disease Education Program (NKDEP) announced today the availability of a "Nephrology Consult Letter Template", a new web-based tool to improve coordination of care for kidney patients.

Chronic kidney disease (CKD) - affecting approximately 20 million Americans - has reached epidemic proportions, and the number of people in the United States who go on to develop kidney failure has doubled each of the last two decades. This trend is likely to continue, leaving nephrologists with too many patients to manage alone.

Anticipating the shortage, nephrologists are turning to primary care providers (PCPs) for help. PCPs make logical partners since they usually are the first to see kidney patients. But agreeing early-on about who will handle what aspects of care will be critical to establishing and maintaining good partnerships and providing high-quality care to patients.

The "Nephrology Consult Letter Template" is on both the RPA and NKDEP websites at <http://www.renalmd.org> and <http://www.nkdep.nih.gov> respectively.

NEW METHOD TO IDENTIFY BLOOD PROTEINS MAY SPUR NOVEL DISEASE MARKER DISCOVERIES Using conventional technologies, researchers supported by the National Cancer Institute (Science Applications International Corporation-Frederick, Inc. (SAIC)) have developed a new method for identifying proteins found in trace quantities in the blood.* The method offers hope for detecting tiny amounts of these blood-borne molecules that signal the presence of certain diseases, such as cancer, infectious diseases, behavioral disorders, developmental defects, and neurodegenerative diseases. These molecules might be useful biomarkers to aid in earlier detection and treatment of ovarian, breast, and prostate cancer. The National Cancer Institute (NCI) is part of the National Institutes of Health (NIH) and is the government's principal agency for cancer research.

Working at the Laboratory of Proteomics and Analytical Technologies at NCI-Frederick, Md., the researchers crafted a multi-step procedure for separating blood proteins derived from serum, which is the clear, yellowish liquid that separates out from blood after clotting and does not contain any cells. Together, all of these proteins are known as the serum proteome. Prior efforts to identify low-abundance proteins were not as successful mainly because separation steps to reduce amounts of large, high-abundance proteins caused a simultaneous loss of the smaller, low-abundance proteins. Separation and fractionation are needed to produce samples that can be analyzed by mass spectrometry, a high-throughput technique for identifying individual proteins.

To address this problem, the researchers performed a series of fractionations on a tiny volume of serum - about 0.04 teaspoons. The steps included several different methods of separation, called isoelectric focusing and chromatography, that are based on the size, electric charge, and other chemical properties that differ between proteins. These samples were then injected onto a mass spectrometer to acquire the raw sequence data that was subsequently linked to a human proteomic database to identify the observed molecules.

The researchers created a publicly available database of the newly identified human blood proteins. Located online at <http://bpp.nci.nih.gov> the database will serve as a resource for other investigators studying blood proteins. For more information about cancer, please go to <http://cancer.gov>

HHS Report to Congress on Autism Activities (*PDF file, 14 pages)
<http://www.nimh.nih.gov/autismiacc/autismreport2004.pdf>

CONGRESSIONAL APPROPRIATIONS COMMITTEE REPORT ON THE STATE OF AUTISM RESEARCH AND AUTISM RESEARCH MATRIX (PDF file, 31 pages)
<http://www.nimh.nih.gov/autismiacc/CongApprCommRep.pdf>

USE OF ANTIDEPRESSANTS IN YOUNG PEOPLE The National Institute of Mental Health (NIMH) has reviewed the best current information about treatment of depression to assist parents and caretakers in making treatment choices.
<http://www.nimh.nih.gov/press/StmntAntidepmeds.cfm>

EMOTION-REGULATING PROTEIN LACKING IN PANIC DISORDER
<http://www.nimh.nih.gov/events/prPanicReceptor.cfm> Three brain areas of panic disorder (<http://www.nimh.nih.gov/anxiety/panicmenu.cfm>) patients are lacking in a key component of a chemical messenger system that regulates emotion, researchers at the NIH's National Institute of Mental Health (NIMH) have discovered. Brain scans revealed that a type of serotonin receptor is reduced by nearly a third in three structures straddling the center of the brain. The finding is the first in living humans to show that the receptor, which is pivotal to the action of widely prescribed anti-anxiety medications, may be abnormal in the disorder, and may help to explain how genes might influence vulnerability. Drs. Alexander Neumeister and Wayne Drevets, NIMH Mood and Anxiety Disorders Program, and colleagues, report on their findings in the January 21, 2004 "Journal of Neuroscience".

NIMH grantee Dr. Rene Hen, Columbia University, and colleagues, reported in 2002 that a strain of gene "knockout" mice, engineered to lack the receptor during a critical period in early development, exhibit anxiety traits in adulthood (<http://www.nimh.nih.gov/events/prrescuedmice.cfm>), such as a reluctance to begin eating in an unfamiliar environment. More recent experiments with the knockout mice show that a popular SSRI (serotonin selective reuptake inhibitor <http://www.nimh.nih.gov/publicat/medicate.cfm>) drug produces its anti-anxiety effects by stimulating the formation of new neurons in the hippocampus via the serotonin 5-HT1A receptor.
<http://www.nimh.nih.gov/events/prneurogenesis.cfm>

In the current study, Neumeister and Drevets used PET scans (positron emission tomography - <http://www.nimh.nih.gov/hotsi/petscan.htm>) to visualize 5-HT1A receptors in brain areas of

interest in 16 panic disorder patients - seven of whom also suffered from major depression - and 15 matched healthy controls. A new radioactive tracer (FCWAY), developed by NIH Clinical Center PET scan scientists, binds to the receptors, revealing their locations and a numerical count by brain region. Subjects also underwent structural MRI (magnetic resonance imaging) scans, which were overlaid with their PET scan data to precisely match it with brain structures.

In the panic disorder patients, including those who also had depression, receptors were reduced by an average of nearly a third in the anterior cingulate in the front middle part of the brain, the posterior cingulate, in the rear middle part of the brain, and in the raphe, in the midbrain. Previous functional brain imaging studies have implicated both the anterior and posterior cingulate in the regulation of anxiety. Stimulation of 5-HT1A receptors in the raphe regulates serotonin synthesis and release. In an earlier PET study of depressed patients, using a different tracer, Drevets and colleagues found less dramatic reductions of the receptor in the anterior and posterior cingulate, but a 41 percent reduction in the raphe. These findings add to evidence for overlap between depression and anxiety disorders.

Although animal experiments have shown that cortisol secretion triggered by repeated stress reduces expression of the gene that codes for the 5-HT1A receptor, such stress hormone elevations are usually not found in panic disorder. Noting the recent discovery of a variant of the 5-HT1A receptor gene linked to major depression and suicide, the researchers suggest that reduced expression of the receptor "may be a source of vulnerability in humans, and that abnormal function of these receptors appears to specifically impact the cortical circuitry involved in the regulation of anxiety."

Other researchers who participated in the study are Drs. Earle Bain, Allison Nugent, Omer Bonne, David Luckenbaugh, Dennis Charney, NIMH; Richard Carson, William Eckelman, Peter Herscovitch, Warren G. Magnuson Clinical Center.

ARCHIVED ISSUES OF TSC ALERT:

December 2002 TSC Alert

<http://www.tsalliance.org/research/tsc%20alert.asp>

January 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alert012203.asp>

February 2003 TSC Alert

<http://www.tsalliance.org/Research/TSC%20Alert021003.asp>

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