

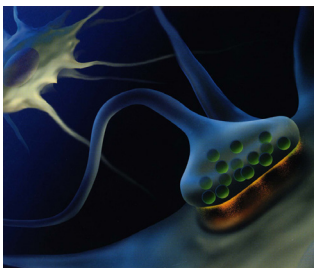


Volume 11, Issue 2, Fall 2012

Waggoner Center for Alcohol &amp; Addiction Research Newsletter

## Our Mission

To develop solutions for the prevention and cure of alcoholism and related illnesses.



Above (left to right):

Richard Morrisett,  
 Hitoshi Morikawa,  
 John Mihic,  
 Adron Harris,  
 Igor Ponomarev,  
 Yuri Blednov,  
 and Dayne Mayfield

Photo by Joshua Russell

## Novel Approaches for Alcoholism Medication Development

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has awarded a collaborative program project grant (PO1) to the Waggoner Center to research the neurobiology of alcohol dependence, with emphasis on the development of novel therapeutics and identification of new therapeutic targets and approaches. The program consists of three research projects supported by common administrative and animal cores.

The three studies will identify and characterize 1) peptides that modulate the functioning of cell membrane proteins (ion channels), 2) epigenetic enzyme inhibitors, and 3) microRNAs (miRNAs) that regulate gene expression. **S. John Mihic**, Associate Professor of Neurobiology, and **Richard Morrisett**, Professor of Pharmacology and Toxicology, are conducting the peptide study, **Igor Ponomarev**, Research Assistant Professor of Pharmacy, and **Hitoshi Morikawa**, Associate Professor of Neurobiology, head the epigenetic study, and **R. Dayne Mayfield**, Research Scientist, leads the miRNA research. **Yuri Blednov**, Research Scientist, and **Rueben Gonzales**, Professor of Pharmacology and Toxicology, run the animal core, providing common animal

models for all three projects. Identical, global behavioral measurements and drug treatments will allow direct comparison of results among projects. **R. Adron Harris**, director of the Waggoner Center, is the principal investigator, supervising all research and testing.

*Mihic/Morrisett project* - Alcohol modulates neuronal activity by binding to a variety of ion channels that are thought to be plausible alcohol targets, such as the glycine receptor, a key component of inhibitory neurotransmission in brain and spinal cord. To better understand the binding mechanisms involved, Mihic will identify peptides that bind with specificity to the glycine receptor using a technique called phage display. A phage (or bacteriophage) is a virus that infects bacteria, and its genetic material can be modified to express a unique surface coat peptide. Approximately two billion slightly different phages (collectively called a phage library) will be introduced to a population of glycine receptors to isolate the few phages whose unique coat peptides allow them to specifically bind to the receptor. Mihic and Morrisett will then assess synthesized peptides as allosteric modulators of glycine receptor function. Those peptides found



## Medication Development (Cont'd)

to alter channel function, or alcohol effects on channel function, will be tested in animal models in alcohol preference and consumption studies to establish their possible therapeutic effectiveness.

*Ponomarev/Morikawa project* - Studies of brain gene expression (transcriptome profiles or the levels of mRNA molecules present in a cell) in human alcoholics and animal models show coordinated regulation of many genes. Some of these transcriptome changes are the result of epigenetic modifications. Transcription or repression of a specific gene is determined by the conformational state of chromatin (the complex of chromosomal DNA and proteins) and by the recruitment of transcription factors to DNA regulatory sites. Both DNA and structural proteins of chromatin - histones - can be chemically modified by different enzymes (epigenetic modifications), which may change gene expression. Chronic alcohol abuse can promote some of the epigenetic modifications, thus influencing gene expression and changing brain functions. Small molecule inhibitors of enzymes that modify chromatin and produce epigenetic modifications are also known as epigenetic drugs. Ponomarev and Morikawa will test the effects of epigenetic drugs, histone deacetylase inhibitors (HDACi) and DNA methyl-

transferase inhibitors (DNMTi), on alcohol behaviors in mice. Those drugs that produce changes in alcohol consumption will be tested on gene expression and cellular physiology in the brain reward pathway. Integration of animal behavior, cell physiology and gene expression data will elucidate the drugs' mechanisms of action and identify novel targets for drug development.

*Mayfield project* - Chronic alcohol abuse produces lasting changes in brain function such as tolerance, physical dependence, and craving. The Mayfield project will test the overall hypothesis that these changes are due to the coordinated regulation of alcohol-responsive genes by small non-coding miRNAs. These molecules are post-transcription epigenetic modifiers that bind to messenger RNAs in the cytoplasm, usually resulting in translational repression or target degradation and gene silencing. Using next generation sequencing, Mayfield will define miRNA changes in brains of mice consuming alcohol and will test the importance of these constructs by measuring alcohol consumption and reward behaviors after delivery of miRNAs to brain. This study will identify key regulatory elements and provide new insight regarding the role of miRNAs in regulation of brain function and alcohol abuse.

## HONORS & AWARDS

The university awarded undergraduate **Lindsay Becker** (Pierce-Shimomura Lab) the Louis M. Pearce, Jr., Unrestricted Endowed Presidential Scholarship, a highly competitive award given to 100-150 students annually. Additionally, Lindsay, lab mate **Kristin Ward**, and Harris Lab student **Ui (Danny) S. Lee** received University Research Awards from the Office of the Vice President for Research to help fund their research projects. Danny also received two awards for travel to scientific meetings from the College of Natural Sciences and the Society for Neuroscience.

The School of Biological Sciences gave its first annual "High Flyer Award" to **Rebecca Howard**, PhD (Harris Lab), and **Andrés Vidal Gadea**, PhD (Pierce-Shimomura Lab), to support postdoctoral travel to professional meetings.

Recipients of the National Research Service Award (NRSA) from The National Institutes of Health:

**Linzy Hendrickson**, PhD, (Morikawa Lab), "Regulation of Ethanol Intake by Prior Feeding: D2 Autoinhibition in VTA"

**Scott Davis** (Pierce-Shimomura Lab), "The Molecular Basis for the Action of Ethanol on the BK Channel"

**Ben Lovely**, PhD, (Eberhart Lab), "Ethanol-induced Lower Jaw Loss in BMP Signaling Pathway Mutants"

Doctoral degrees awarded:

**Zachary Jeanes**, PhD (Morrissett Lab), Jul. 12, 2012  
"Mesocorticolimbic Adaptations In Synaptic Plasticity Underlie The Development Of Alcohol Dependence"

**Leslie Ramsey Whitaker**, PhD (Morikawa Lab), Aug. 2, 2012  
"Social Isolation Enhances Calcium Signaling and Synaptic Plasticity in Dopamine Neurons of the Ventral Tegmental Area"



**Graduate School Outreach Program**

*Photo by Marsha Miller*

Joshua Russell, center, graduate student in the Pierce-Shimomura lab, conceived and developed the UT Graduate Science Education Outreach group. Their first project - *Present your PhD thesis to a 12-year-old* - brings doctoral candidates to middle school classrooms in support of science education in the Austin community. Inspiration for the program came after Josh delivered a well-received presentation of his thesis, aided by sign language, to ninth-grade students at the Texas School for the Deaf. Approximately 20 graduate students in the sciences currently participate in the group, which may one day include students from all graduate programs at the university. The program is also expanding to work with local clubs, camps, festivals, high schools, and community colleges, quickly becoming a model of cross-educational cooperation and opportunity.



Photo by Alex Wang, courtesy of the College of Natural Sciences

**Caitlin Taylor**, former undergraduate in the Pierce-Shimomura lab, was one of the 2012 Dean's Honored Graduates in the College of Natural Sciences. Considered the college's highest honor accorded to graduating seniors, the award recognizes independent research with significant scientific impact, as well as service and leadership within the college and university communities. Her honors thesis, "Prevention of neurodegeneration in a *C. elegans* model of Parkinson's disease," contributed to revisions of a previously published paper by another research group and provided new insights regarding the work of a Nobel prize-winning team of investigators. Caitlin began her graduate studies in neuroscience at Stanford University School of Medicine this fall.



Photo by Marsha Berkman

**Da'Marcus Baymon** (Mihic Lab) received the 2012-2013 Outstanding Student Award from the Texas Parents association, part of the Division of Student Affairs. Each year the award recognizes two undergraduate students (one male, one female) distinguished by leadership, scholarship, character, and service. A lead mentor and chemistry tutor with the university's Texas Interdisciplinary Plan Mentor Academy, Da'Marcus has helped more than 500 freshmen successfully transition to the university environment through participation in small academic communities. In the Mihic Lab, he is characterizing a novel *Drosophila* ion channel that is a member of the GABA-A/glycine receptor superfamily of receptor subunits. He is currently applying to medical school for Fall 2013.

## PUBLICATIONS

Bittner G. D., Keating C. P., Kane J. R., Britt J. M., Spaeth C. S., Fan J. D., Zuzek A., Wilcott R. W., Thayer W. P., Winograd J. M., Gonzalez-Lima F., **Schallert T.** (2012). Rapid, effective, and long-lasting behavioral recovery produced by microsutures, methylene blue, and polyethylene glycol after completely cutting rat sciatic nerves. *J Neurosci Res* 90: 967-980.

**Blednov Y. A., Mayfield R. D.,** Belknap J., **Harris R. A.** (2012). Behavioral actions of alcohol: phenotypic relations from multivariate analysis of mutant mouse data. *Genes Brain Behav* 11: 424-435.

**Blednov Y. A., Ponomarev I.,** Geil C., Bergeson S., Koob G. F., **Harris R. A.** (2012). Neuroimmune regulation of alcohol consumption: behavioral validation of genes obtained from genomic studies. *Addict Biol* 17: 108-120.

Borghese C. M., Xiong W., Oh S. I., Ho A., **Mihic S. J.,** Zhang L., Lovinger D. M., Homanics G. E., Eger E. I., 2nd, **Harris R. A.** (2012). Mutations M287L and Q266I in the Glycine Receptor alpha1 Subunit Change Sensitivity to Volatile Anesthetics in Oocytes and Neurons, but Not the Minimal Alveolar Concentration in Knockin Mice. *Anesthesiology* 117: 765-771.

Brager D. H., Akhavan A. R., **Johnston D.** (2012). Impaired dendritic expression and plasticity of h-channels in the *fmr1*(-/y) mouse model of fragile X syndrome. *Cell Rep* 1: 225-233.

Khaing Z. Z., Geissler S. A., Jiang S., Milman B. D., Aguilar S. V., Schmidt C. E., **Schallert T.** (2012). Assessing forelimb function after unilateral cervical spinal cord injury: novel forelimb tasks predict lesion severity and recovery. *J Neurotrauma* 29: 488-498.

Krishnan H. R., Al-Hasan Y. M., Pohl J. B., Ghezzi A., **Atkinson N. S.** (2012). A role for dynamin in triggering ethanol tolerance. *Alcohol Clin Exp Res* 36: 24-34.

## Building a Partnership

Individual, foundation and corporate support is essential to the continued growth and success of this world-class research center. To support the Waggoner Center for Alcohol and Addiction Research, please visit:

[utdirect.utexas.edu/apps/utgiving/online/nlogon/?menu1=NSWC](http://utdirect.utexas.edu/apps/utgiving/online/nlogon/?menu1=NSWC)

or call: 512-471-3299

or contact:

UT Austin Development Office  
College of Natural Sciences  
Office of the Dean  
1 University Station G2500  
Austin, TX 78712-0548



THE UNIVERSITY OF TEXAS AT AUSTIN

## Waggoner Center

for Alcohol & Addiction Research

[utexas.edu/research/wcaar/](http://utexas.edu/research/wcaar/)

2500 Speedway

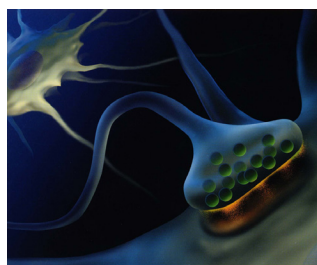
MBB 1.124

Austin, Texas 78712

USA

Tel: 512-232-2520

Fax: 512-232-2525



### Proclivitas

### Waggoner Center for Alcohol & Addiction Research Newsletter

The Waggoner Center for Alcohol and Addiction Research was established in 1999 at The University of Texas at Austin. The Center was made possible by a donation from M. June and J. Virgil Waggoner and matching funds from UT Austin. The mission of the Center is to create a premier research center for alcohol and addiction research, thereby developing solutions for the prevention and cure of these diseases.

#### Director:

R. Adron Harris, Ph.D.

#### Editing/Design:

Marsha Berkman, Debbie James

#### Many thanks to:

John Mihic, Igor Ponomarev, Dayne Mayfield, and Lee Clippard

#### Comments:

[berkman@austin.utexas.edu](mailto:berkman@austin.utexas.edu)

### PUBLICATIONS (Cont'd)

Lee B. K., Iyer V. R. (2012). Genome-wide Studies of CCCTC-binding Factor (CTCF) and Cohesin Provide Insight into Chromatin Structure and Regulation. *J Biol Chem* 287: 30906-30913.

Mangieri R. A., Cofresi R. U., Gonzales R. A. (2012). Ethanol seeking by Long Evans rats is not always a goal-directed behavior. *PLoS ONE* 7: e42886. doi:10.1371/journal.pone.0042886

Ni Y., Weber Hall A., Battenhouse A., Iyer V. R. (2012). Simultaneous SNP identification and assessment of allele-specific bias from ChIP-seq data. *BMC Genet* 13: 46. doi:10.1186/1471-2156-13-46

Nunez Y. O., Mayfield R. D. (2012). Understanding Alcoholism Through microRNA Signatures in Brains of Human Alcoholics. *Front Genet* 3: 43. doi: 10.3389/fgene.2012.00043

Robinson B. G., Khurana S., Pohl J. B., Li W. K., Ghezzi A., Cady A. M., Najjar K., Hatch M. M., Shah R. R., Bhat A., Hariri O., Haroun K. B., Young M. C., Fife K., Hooten J., Tran T., Goan D., Desai F., Husain F., Godinez R. M., Sun J. C., Corpuz J., Moran J., Zhong A. C., Chen W. Y., Atkinson N. S. (2012). A low concentration of ethanol impairs learning but not motor and sensory behavior in *Drosophila* larvae. *PLoS ONE* 7(5): e37394. doi:10.1371/journal.pone.0037394

Schier C. J., Mangieri R. A., Dilly G. A., Gonzales R. A. (2012). Microdialysis of Ethanol During Operant Ethanol Self-administration and Ethanol Determination by Gas Chromatography. *J Vis Exp* (67) e4142. doi: 10.3791/4142

Swartz M. E., Nguyen V., McCarthy N. Q., Eberhart J. K. (2012). Hh signaling regulates patterning and morphogenesis of the pharyngeal arch-derived skeleton. *Dev Biol* 369: 65-75.

Tipps M. E., Iyer S. V., Mihic S. J. (2012). Trifluoroacetate is an allosteric modulator with selective actions at the glycine receptor. *Neuropharmacology* 63:368-373.

Yan J., Aldrich R. W. (2012). BK potassium channel modulation by leucine-rich repeat-containing proteins. *Proc Natl Acad Sci U S A* 109: 7917-7922.