

Volume 11, Issue 1, Spring 2012 Waggoner Center for Alcohol & Addiction Research Newsletter

# **Our Mission**

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



# Above (left to right):

Chang Hoon Lee, W. David Johnson II, Lindsay McCracken

# Scientific Leaders of the Future

The Waggoner Center dedicates considerable resources to the education of future scientific leaders. Below we profile recent trainees as they move forward to postdoctoral and leadership positions in research.

Chang Hoon Lee – Graduate student, Harris & Mayfield labs: Though a single gene usually produces a single protein, different protein isoforms can occur. These isoforms arise from splice variants of the mature messenger RNA (mRNA) synthesized during the process known as gene transcription. Pre-mRNA is made up of segments called exons and introns; since only the exons are necessary in the translation of protein, pre-mRNA is spliced, resulting in mature mRNA that consists of only exons. Splice variants are shorter or longer alterations of the remaining exons that make up the mature mRNA. I studied the splice variants that result in gamma-amniobutyric acid type B receptor  $(GABA_{n}R)$  isoforms, which may play a role in the development of alcoholism. Utilizing whole transcriptome sequencing (RNA-seq), a technology that measures the level of mRNA present in a tissue sample, I compared the level of GABA<sub>R</sub>R splice variants in alcoholic brains versus a control group. My study found that chronic alcohol exposure altered exon/intron

expression, which may diminish the normal  $GABA_BR$  population and compromise normal neurotransmission in alcoholic brains. ¶ *Post-doctoral Fellow, University of California, Los Angeles:* I will begin postdoctoral training in the lab of Dr. Daniel Geschwind this summer, analyzing genome-wide data to find target genes related to autism and neurodegenerative diseases using next generation sequencing.

W. David Johnson II – Postdoctoral fellow, Harris lab: I investigated the unusual way in which alcohol can bind to multiple sites on a single brain protein. Using frog oocyte electrophysiology, I characterized a novel inhibitory site on the GABA, receptor, one of the most important targets for alcohol in the human brain. A better understanding of all relevant binding sites for alcohol will help us identify problematic mutations and develop drugs to counteract conditions such as alcohol use disorders. ¶ Biochemist, Medical Service Corps (MSC), Army Medical Department, US Army: After completing officer training, I'll receive my research assignment, which will support the health of Army personnel and their families. MSC officers, based on the battlefield or in the lab, provide leadership and expertise to the United States

#### Future Leaders (Cont'd)

Joint Strategic Operations Command. Typical biochemistry projects include the development of vaccines and other agents used in defense against bioterrorism.

Lindsay McCracken – Graduate student, Harris lab: Alcohol is only one of many modulators of the glycine receptor, a major inhibitory receptor in the central nervous system. Other modulators include divalent metals such as zinc. I examined how zinc and ethanol might interact in their enhancement of glycine receptor function. Using a whole-cell electrophysiology approach, I first showed that these two compounds have synergistic effects on the glycine receptor and later characterized this in considerable detail using receptor subunit mutagenesis. I also studied the roles of specific amino acids at specific molecular sites that contribute to the formation of alcohol binding pockets with glycine receptors. ¶ Postdoctoral Fellow, Columbia University Medical Center: In Dr. Neil Harrison's lab, I use electrophysiological and molecular techniques to investigate alcohol and anesthetic effects on the glycine receptor and acid-sensing ion channels.

## Rebecca Howard – Postdoctoral Fellow, Harris



*lab:* Building on my background in protein crystallography, I took advantage of recent developments in structural biology to understand how proteins bind to drugs such as alcohol. I worked on a bacterial

protein that is closely related to human alcohol targets, providing a simple model system to investigate the structural basis for alcohol binding. ¶ Assistant Professor, Skidmore College: This fall, I'll join the faculty at a liberal arts college in Saratoga Springs, NY, working with undergraduates to further investigate simple models of drug interactions. We will use frog oocyte electrophysiology to study drug modulation of cell signaling and will collaborate with computational chemists to create novel structural models based on our functional data. I look forward to teaching small classes on chemical principles, biochemistry, and seminar topics related to my research interests, and to participating in Skidmore's residential college community. Jascha Pohl – Graduate student, Atkinson lab:



I studied the role of circadian genes in tolerance to ethanol in the fruit fly *Drosophila melanogaster*. Interestingly, some mutations disrupt tolerance, whereas others do not, indicating that while some

circadian genes are necessary for tolerance, a functioning clock is not necessary. Additionally, I led a team of undergraduates to investigate fly preference of ethanol as a caloric or pharmacological resource. Our results indicated that flies like ethanol because of its value as a food. ¶ *Postdoctoral Fellon, University of California, Berkeley:* I recently joined the lab of Dr. Mark Tanouye, whose lab uses the genetic tools of the fruit fly to study epilepsy. Mutations in the fly can cause them to exhibit seizure-like behaviors, which can be ameliorated by feeding the fly anti-epileptic drugs. I investigate whether mutations that inhibit synaptic functions successfully suppress seizures.

Megan Tipps – Graduate student, Mihic lab:



Unlike most other drugs of abuse, alcohol has multiple targets, resulting in a very complex mechanism of action. I studied how alcohol-induced changes at individual ion channels, specifically the glycine re-

ceptor (GlyR), contribute to the overall effects of alcohol at the behavioral level. GlyR lacks a truly specific modulator, making it difficult to isolate the effects of channel signaling. I used phage display technology to identify small peptides that potentiate GlyR function, similar to the effect of alcohol, without affecting other closely related channel types. Postdoctoral Trainee, Oregon Health & Science University: Dr. Kari Buck's lab works on identification of chromosomal regions and specific genes that contribute to the effects of alcohol. My project involves a gene encoding a subunit of the potassium channel family. Mice lacking the gene show greatly reduced withdrawal responses. I use this genetic model to compare alcohol withdrawal with other alcohol-related behaviors, including fear-based learning and memory and measures of impulsive behavior.

#### **HONORS & AWARDS**

The Midwest Alcoholism Research Center featured **Kim Fromme**, professor of Psychology, as an expert speaker at the 12<sup>th</sup> Annual Guze Symposium on Alcohol, held Feb. 16, 2012, at Washington University School of Medicine in St. Louis, MO. Dr. Fromme spoke about drinking and other behavioral risks spanning high school and college.

The College of Natural Sciences recognized Harris Lab student **Ui** (**Danny**) **S. Lee** as a 2012 Undergraduate Research Forum winner and recipient of an Award for Excellence in Research.

Jessica Hicks (Harris Lab) received an Undergraduate Competitive Travel Award to attend the 2012 Experimental Biology Meeting in San Diego, CA, April 21-25, 2012, sponsored by the American Society for Biochemistry and Molecular Biology.

Doctoral Degrees Awarded

Lindsay McCracken, PhD (Harris Lab), Feb. 6, 2012 "A Critical Role for Zinc in Ethanol Action at the Glycine Receptor"

**Chang Hoon Lee**, PhD (Harris & Mayfield Labs), Nov. 30, 2011 "Splicing of Human GABA<sub>B</sub> Receptor Subunit 1 (GABA<sub>B</sub>1) in Non-Alcoholic and Alcoholic Brains"

#### Jascha Pohl, PhD

(Atkinson Lab), Nov. 29, 2011 "The Role of Circadian Genes in Tolerance to Ethanol in *Drosophila melanogaster*"

#### Megan Tipps, PhD

(Mihic Lab), Jun. 30, 2011 "Identification of Novel Allosteric Modulators of the Glycine Receptor using Phage Display Technology"

#### NEWS - Medication Grant Awarded

The National Institute on Alcohol Abuse and Alcoholism recently awarded a five-year \$3,380,116 Program Project on Alcohol-Related Research (P01) grant to collaborators R. Adron Harris, Yuri Blednov, Reuben Gonzales, R. Dayne Mayfield, S. John Mihic, Hitoshi Morikawa, Richard Morrisett, and Igor Ponomarev. The grant is entitled "Novel molecular and cellular approaches for alchoholism medication development."



## PUBLICATIONS

**Blednov YA**, Benavidez JM, Homanics GE, **Harris RA** (2012). Behavioral characterization of knockin mice with mutations M287L and Q266I in the glycine receptor alpha1 subunit. J Pharmacol Exp Ther 340, 317-329.

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(Publications continued next page.)

#### Westphal Visits

During a visit to the university in March, **Undersecretary of the Army Joseph W. Westphal** (left) met with neuroscience researchers, including R. Adron Harris, Director of the Waggoner Center. Westphal explored labs conducting research that would benefit the Army.

- Photo by Marsha Miller

# 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:

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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

# **Useful Websites**

Addiction Science Research and Education Center <u>utexas.edu/research/asrec</u>

National Institute on Alcohol Abuse and Alcoholism (NIAAA) <u>niaaa.nih.gov</u>

National Institute on Drug Abuse (NIDA) <u>nida.nih.gov</u>

Research Society on Alcoholism (RSA) rsoa.org

International Society for Biomedical Research on Alcoholism (ISBRA) <u>isbra.com</u>

#### The University of Texas at Austin

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Proclivitas

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: Igor Ponomarev, Rebecca Howard & John Mihic

Comments: berkman@austin.utexas.edu

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