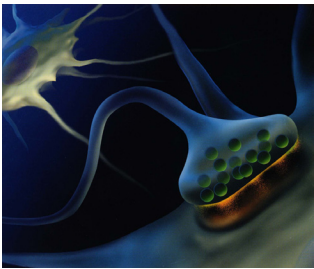


Waggoner Center for Alcohol & Addiction Research

THE UNIVERSITY OF TEXAS AT AUSTIN

Our Mission

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



Above (left to right):
Dr. Naresh Genabai
Megan Tipps
Dr. Giorgio Gorini

Photo credit:
Scott Schulz

CENTER FOR MEDICATION DEVELOPMENT FOR TREATMENT OF ALCOHOLISM

Although alcohol dependence and alcohol abuse severely affect public health at great socioeconomic cost, the Federal Drug Administration has approved only three medications, each with limited efficacy, for the treatment of alcoholism. The National Institute for Alcoholism and Alcohol Abuse awarded a team of investigators led by **Dr. R. Adron Harris**, director of the Waggoner Center for Alcohol & Addiction Research (WCAAR), a P20 grant to address this concern. The grant establishes the Center for Medication Development for Treatment of Alcoholism to advance the rational development of novel therapies for alcoholism. The new Center will develop the technologies and collaborations necessary to discover and validate new alcohol targets and define effective drug treatments.

The Center is comprised of three research components and two pilot projects, in addition to administrative and animal cores. Below we outline projects headed by **Dr. Igor Ponomarev**, research assistant professor of pharmacology and toxicology, **Dr. R. Dayne Mayfield**, research scientist, WCAAR, **Dr. S. John Mihic**, associate professor of neurobiology, **Dr. Nigel Atkinson**, professor of neurobiology, and **Dr. Maria Croyle**, associate professor of pharmaceuticals.

Excessive alcohol consumption precedes the development of alcohol dependence. **Dr. Naresh Genabai**, a postdoctoral fellow, works with Ponomarev to investigate the mechanisms involved in the progression of alcoholism, as controlled alcohol consumption gives way to alcohol abuse and alcohol dependence. By profiling gene expression in dopamine neurons after induction of alcohol dependence, the Ponomarev group is testing the hypothesis that different neuronal populations can be distinguished by their individual patterns of gene expression and by their transcriptional responses to alcohol, which may correlate with cell physiology. The long-term goal of this research is to determine the molecular mechanisms of cellular adaptation to alcohol in individual neuronal populations of cells making up the neurocircuits that mediate alcohol actions.

The Mayfield project expands on the gene expression work by examining changes in protein-protein interactions that underlie alcohol dependence in order to define molecular sites for drug treatment. Mayfield and his postdoctoral fellow **Dr. Giorgio Gorini** are testing ethanol-sensitive "target" proteins. These are proteins being studied by other researchers associated with the Center or represent newer proteins

CENTER FOR MEDICATION DEVELOPMENT (Cont'd)

identified by microarray screens as possibly playing a role in alcohol actions *in vivo*. The target proteins include ion channels required for normal synaptic transmission and membrane trafficking proteins. Since cell physiology depends on protein-protein interactions, the Mayfield group is trying to identify novel protein complexes associated with each of these target proteins in genetically-engineered mice. The Mayfield lab hypothesizes that excessive ethanol consumption alters protein complexes important for normal trafficking and targeting of proteins involved in synaptic transmission.

The reinforcing effects of ethanol most likely arise from a summation of its effects on a number of protein targets, including neurotransmitter receptors and ion channels. Testing peptides selected from a massive peptide display library, **Megan Tipps**, a graduate student in the Mihic lab, hopes to identify specific peptides that affect brain receptors thought to be critical for alcohol

actions. She aims to identify peptides that selectively mimic or block alcohol actions on two specific protein targets, heteromeric alpha1/beta glycine receptors and heteromeric NR1/2B NMDA receptors. These proteins are thought to mediate some of the affects of ethanol *in vivo*; they also exhibit considerable sensitivity to the effects of alcohol *in vitro*.

Following identification of peptides, Tipps will characterize the peptides functionally. The hypothesis to be tested is that peptides can be identified that either partially or completely block alcohol actions on protein targets without markedly changing the functional properties of those targets in the absence of ethanol. She will also test the most promising peptides on receptors expressed in neuronal cells and initiate mutagenesis studies to determine the critical amino acids residues of specific glycine receptor peptides that mediate their effects on the receptor.



Above:
Rudi Bohm

Photo credit:
Dr. Nigel Atkinson

The Atkinson pilot project will validate a putative alcohol site *in vivo*. The function of the NMDA receptor is inhibited by alcohol and organic solvent anesthetics. Amino acid residues within the TM3 domain of the receptor play a role in this inhibition. A change of a phenylalanine to alanine at position 639 within TM3 eliminates inhibition by some anesthetics and reduces the efficacy of alcohol inhibition in *Xenopus* oocytes. If this inhibition of the NMDA receptor contributes significantly to sedation, then one would predict that an animal carrying this mutation would be resistant to sedation. **Rudi Bohm**, a research associate working with Atkinson, will establish a connection between an amino acid change and an alcohol behavior in fruit flies carrying a NMDA receptor NR1 gene mutation. These fruit flies, or *Drosophila*, provide a low-cost, high-throughput screening alternative to genetically-engineered mice.

Bohm and Atkinson will use *Drosophila* gene knock-in technology to generate flies carrying the F639A mutation within the NR1 receptor gene.

They will examine the flies to determine if the mutation reduces the sensitivity to sedation with alcohol and if the mutation affects the capacity of flies to acquire functional behavioral tolerance to ethanol. Following this pilot study, the investigators will correlate oocyte electrophysiological data on the effects of alcohol and anesthetics to whole animal behavioral data in flies.

In the second pilot project, **Dr. Maria Croyle** will use her expertise in gene therapy to employ a novel method for delivering genes to mouse brain after intravenous injection. This new approach will greatly facilitate testing of targets of alcohol action by 'knockdown' of these proteins in brain by the delivery of inhibitory RNAs (RNAi or shRNA). In addition, it provides an opportunity to deliver microRNAs or protein-coding RNAs for gene therapy and may have applications beyond alcoholism. Administration of these viral particles to mice will produce gene inhibition throughout the central nervous system and presumably produce a behavioral change to the effects of alcohol.

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:

www.cns.utexas.edu/development/outright.asp

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

www.utexas.edu/research/wcaar

HONORS & AWARDS

The National Institutes of Health (NIH) awarded **Dr. Juan Dominguez**, assistant professor of psychology, an R21 grant to study the role of the hypothalamus in gender-sensitive response to cocaine administration. The two-year project received a budget of \$181,680.

Dominquez noted in his proposal that while epidemiological data show that more men than women abuse cocaine, preclinical and clinical evidence indicate that females are more vulnerable to its psychostimulant effects. Evidence also indicates that estrogen is at least partly responsible for this difference in sensitivity. Most studies point to the striatum and nucleus accumbens (NAcc) as brain areas on which estrogen acts to produce this gender difference. However, one area receiving little attention as potentially important for mediating this effect is the medial preoptic area (MPOA). Highly sensitive to estrogen activity, the MPOA is sexually dimorphic

and plays a role regulating naturally rewarding behaviors. These attributes make the MPOA a likely candidate at which estrogen might act to mediate gender-sensitive differences in responses to cocaine, though little is known about its role in this effect. Using neuroanatomical, neurochemical, and behavioral assays, the project will examine whether estrogen enhances the female response to cocaine via the MPOA. The planned experiments will also contribute to a more complete understanding of how hypothalamic mechanisms, especially those highly sensitive to gonadal signals, may affect response to cocaine use. Finally, the study will help us better understand the neuroendocrine regulation of gender-sensitive differences in response to cocaine by exploring a possible new mechanism mediating this effect. Such an understanding may be beneficial when designing treatments for addiction, when gender-sensitive differences are especially important.

NIAAA CELEBRATES 40TH ANNIVERSARY

The National Institute of Alcohol Abuse and Alcoholism (NIAAA) was established on December 31, 1970, during the Nixon administration. The Institute plans to mark the anniversary with commemorative banners installed on the main NIH campus, anniversary issues of NIAAA publications *Alcohol Alert* and *Alcohol Research & Health*, and a symposium. Additionally, a website redesign and branding effort will help increase recognition of the Institute and its products. Please visit the NIAAA website for updates regarding activities celebrating 40 years of alcohol research.

Dr. Carlton K. Erickson, associate dean for research and graduate studies, College of Pharmacy, received the John P. McGovern Award for Excellence in Medical Education. Presented at the annual meeting of the Association for Medical Education and Research in Substance Abuse (AMERSA) in November, the honor is the highest award presented by the organization.

Dr. Kim Fromme, professor of psychology, has been appointed to the Scientific Advisory Council for ABMRF: The Foundation for Alcohol Research. For over a quarter century, ABMRF has funded research and communicated results to help build a base of knowledge regarding how alcohol affects health, its use in society, and the benefits

and detriments related to alcohol consumption.

NATIONAL RESEARCH SERVICE AWARDS FOR PREDOCTORAL FELLOWS

Lindsay McCracken (Harris Lab)
The Combined Effects of Zinc and Ethanol at the Glycine Receptor

Megan Tipps (Mihic Lab)
Using Phage Display to Identify Novel Modulators of Ethanol Targets

DOCTORAL DEGREES AWARDED

Dr. Brian Welsh (Mihic Lab), January 22, 2010
Activation and Allosteric Modulation of the $\alpha 1$ Glycine Receptor

PUBLICATIONS

Blednov YA, Walker DL, Iyer SV, Homanics G, **Harris RA** (2009). Mice lacking Gad2 show altered behavioral effects of ethanol, flurazepam and gabaxadol. *Addict Biol* 15:45-61.

Brister HA, Wetherill RR, **Fromme K** (2009). Anticipated versus actual alcohol consumption during 21st birthday celebrations. *J Stud Alcohol Drugs* 71:180-183.

Carrillo J, Howard EC, Moten M, Houck BD, Czachowski CL, **Gonzales RA** (2009). A three-day exposure to 10% ethanol with 10% sucrose successfully initiates ethanol self-administration. *Alcohol* 42:171-178.

DeLorbe JE, Clements JH, Teresk MG, Benfield AP, Plake HR, Millspaugh LE, **Martin SF** (2009). Thermodynamic and structural effects of conformational constraints in protein-ligand interactions. Entropic paradox associated with ligand preorganization. *J Am Chem Soc* 131:16758-16770.

Gorini G, Ponomareva O, Shores KS, Person MD, **Harris RA**, **Mayfield RD** (2010). Dynamin-1 co-associates

Useful Websites

Addiction Science Research and Education Center
www.utexas.edu/research/asrec

National Institute on Alcohol Abuse and Alcoholism (NIAAA)
www.niaaa.nih.gov

National Institute on Drug Abuse (NIDA)
www.nida.nih.gov

Research Society on Alcoholism (RSA)
www.rsoa.org

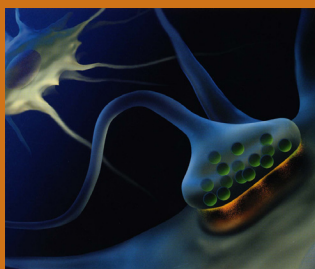
International Society for Biomedical Research on Alcoholism (ISBRA)
www.isbra.com

Waggoner Center

for Alcohol & Addiction Research

The University of Texas at Austin
2500 Speedway, MBB 1.124
Austin, Texas 78712
USA

Tel: 512-232-2520
Fax: 512-232-2525



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.

Editors:

Marsha Berkman
Debbie James
John Mihic

Design:

Kristina Schlegel

Comments:

berkman@mail.utexas.edu

PUBLICATIONS (Cont'd)

with native mouse brain BKCa channels: proteomics analysis of synaptic protein complexes. *FEBS Lett* 584:845-851.

McCracken LM, McCracken ML, Gong DH, Trudell JR, **Harris RA** (2010). Linking of glycine receptor transmembrane segments three and four allows assignment of intra-subunit-facing residues. *ACS Chemical Neuroscience* (in press).

McDaniell R, Lee BK, Song L, Liu Z, Boyle AP, Erdos MR, Scott LJ, Morken MA, Kucera KS, Battenhouse A, Keefe D, Collins FS, Willard HF, Lieb JD, Furey TS, Crawford GE, **Iyer VR**, Birney E (2010). Heritable individual-specific and allele-specific chromatin signatures in humans. *Science*, March 18 epub.

Methner DN, **Mayfield RD** (2010). Ethanol alters endosomal recycling of human dopamine transporters. *J Biol Chem*, 285(14):10310-7.

Ponomarev I, Rau V, Eger EI, **Harris RA**, Fanselow MS (2010). Amygdala transcriptome and cellular mechanisms underlying stress-enhanced fear learning in a rat model of post-traumatic stress disorder. *Neuropsychopharmacology*, Feb 10 epub.

Seidlits SK, Khaing ZZ, Petersen RR, Nickels JD, Vanscoy JE, **Shear JB**, Schmidt CE (2010). The effects of hyaluronic acid hydrogels with tunable mechanical properties on neural progenitor cell differentiation. *Biomaterials* 31:3930-3940.

Stappenbeck CA, **Fromme K** (2010). A longitudinal investigation of heavy drinking and physical dating violence in men and women. *Addict Behav* 35:479-485.

Todorovic J, Welsh BT, Bertaccini EJ, Trudell JR, **Mihic SJ** (2010). Disruption of an inter-subunit electrostatic bond is a critical step in glycine receptor activation. *Proc Natl Acad Sci USA* (in press).

Vaughan EL, Corbin WR, **Fromme K** (2009). Academic and social motives and drinking behavior. *Psychol Addict Behav* 23:564-576.

Westerman AT, Roma PG, Price RC, **Dominguez JM** (2010). Assessing the role of the medial preoptic area in ethanol-induced hypothermia. *Neurosci Lett*, Mar 17 epub.