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

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 pharmaceutics.

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.

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.
identified by microarray screens as possibly playing a role in alcohol actions \textit{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, \textbf{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 effects of ethanol \textit{in vivo}; they also exhibit considerable sensitivity to the effects of alcohol \textit{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.

The Atkinson pilot project will validate a putative alcohol site \textit{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 \textit{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. \textbf{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 \textit{Drosophila}, provide a low-cost, high-throughput screening alternative to genetically-engineered mice.

Bohm and Atkinson will use \textit{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, \textbf{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.
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. Dominionguez 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.

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 a1 Glycine Receptor

PUBLICATIONS


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.rsaoa.org

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

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.

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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.

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**PUBLICATIONS (Cont’d)**


