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Waggoner Center for Alcohol & Addiction Research Newsletter

Our Mission

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



Above (back row): Ben Lovely, Mickaël Degoulet, Yury Núñez (middle row): Regina Mangieri, Rebecca Howard, Giorgio Gorini, Naresh Genabai (front row): Sangeetha Iyer, W. David Johnson II Not pictured: Luisa Scott

> Photo credit: Scott Schultz

Waggoner Center Postdoctoral Research

Postdoctoral fellows perform much of the "heavy lifting" in research labs, conducting original research and writing up the results for publication. Representing different parts of the world and employing varied research methods, these investigators comprise a global approach to the study of addiction.

Mickaël Degoulet (Morikawa Lab), U. Aix-Marseille - Extended activation, or the long-term potentiation (LTP), of a neuronal pathway of glutamate synapses is a well-known mechanism required to encode and store learning and memory. This is a form of "plasticity," where synaptic transmission is enhanced or attenuated in response to stimuli. Natural (food, water) and artificial (drugs of abuse) rewards promote LTP to establish powerful associations between the reward and the environment in which the reward is encountered. I study how repeated exposure to psychostimulants, such as cocaine or amphetamines, produces persistent potentiation of signal transmission - mediated by NMDA glutamatergic receptors - in dopaminergic (DA) neurons of the ventral tegmental area (VTA), a region of the midbrain implicated in addiction. This specific LTP requires both activation of calcium signaling and the NMDA receptors themselves in an induction protocol that may resemble the activity pattern experienced during cue-reward conditioning. Thus, the goal of my project is to define the contribution of NMDA receptor plasticity and voltage-gated calcium ion channels in VTA DA neurons to the learning of drug-associated environmental cues.

Naresh Genabai (Ponomarev Lab), U. Louisiana, Monroe - Dopaminergic neurons (DA) of the ventral tegmental area (VTA) play a critical role in motivation, reward and drug addiction. These DA neurons send projections to several forebrain regions of the motive/reward circuit, where dopamine release has been associated with reward learning and craving. Studies have shown that these dopamine neurons, which project to different areas of the brain, have distinct intrinsic properties and are differentially regulated by neurotransmitter inputs and addictive drugs. My research investigates the hypothesis that these specific VTA DA neurons exhibit distinct genetic responses to alcohol. The identification of cell type specific alcohol-sensitive genes and gene products could provide potential therapeutic targets for alcoholism.

Giorgio Gorini (Mayfield Lab), U. Sassari - My project focuses on the identification of synaptic alcohol-sensitive protein complexes, and the goal is to evaluate the effect of excessive alcohol consumption on resulting protein complexes. Proteinprotein interactions underlie cellular function of brain signaling systems, and examining their possible changes could ultimately help to define new molecular sites for therapeutic interventions. **Rebecca Howard** (Harris Lab), UCSF - I apply new advances in structural biology to understand the molecular basis for alcohol binding in brain proteins. Recent atomic-resolution structures of ion channels related to GABA receptors, as well as new evidence for the interaction of ion channels with membrane lipids, aid in the characterization of alcohol interactions with proteins in unprecedented detail. Using frog oocytes as simple models of neurons, I make targeted mutations and look for changes in alcohol modulation. Combined with molecular modeling, these experiments help elucidate general biophysical principles of alcohol binding, as well as specific characteristics of binding sites in important brain targets.

Sangeetha Iyer (Mihic Lab), U. Pittsburg – Different subtypes of the GABA(A) receptor, a protein involved in inhibitory neurotransmission, are considered targets for alcohol actions, including anxiolysis, motor incoordination, sedation to chronic alcohol addiction and tolerance. My project involves identification of novel peptide modulators of various GABA(A) receptor subtypes in order to delineate their individual contributions to alcohol actions. Application of such peptides *in vivo* may yield information about new therapeutic targets for alcohol addiction treatment.

W. David Johnson II (Harris Lab), Howard U. – I am characterizing a putative inhibitory alcohol site on subunits of the GABA(A) receptor. This protein is implicated in behavioral effects of alcohol and susceptibility to alcoholism. Previous studies have demonstrated discrete molecular sites in alcohol enhancement and in inhibition of GABA (A) receptors. My project tested a proposed alcohol inhibitory site using site-directed mutagenesis and electrophysiology. Results provide direct evidence of an inhibitory alcohol site in GABA (A) receptor subunits, which supports the idea of counteracting sites of alcohol on ligand-gated ion channels.

Ben Lovely (Eberhart Lab), U. Louisville - Our lab studies how genetics and the environment influence the cellular mechanisms underlying craniofacial development. The development and morphogenesis of this structure requires intricate control of several cellular processes including cell movement, signaling and differentiation. Using zebrafish as a model, we study how these processes integrate and how perturbations in these processes lead to craniofacial disease. Through our genetic screens, we have shown that ethanol genetically interacts with several signaling pathways in craniofacial morphogenesis leading to distinct craniofacial defects. My work focuses on exploring these ethanol / gene interactions. I am working to elucidate the genetic predispositions and cellular mechanisms perturbed by ethanol specifically within the Bone morphogenetic protein pathway and how this leads to craniofacial defects. Our work will provide candidate genes for understanding the factors associated with ethanol-induced craniofacial diseases, including Fetal Alcohol Syndrome.

Regina Mangieri (Gonzales Lab), UC, Irvine - I develop animal models of alcohol self-administration that produce alcohol-related behaviors similar to those seen in humans. Current theories of addiction postulate that prolonged drug or alcohol self-administration resembles habitual, rather than goal-directed behavior. I've developed new models of alcohol self-administration in rats that produce either habitual or goal-oriented alcohol seeking. My research suggests that the way an animal learns about the relationship between its behavior and alcohol reinforcement biases the animal toward either goal-directed or habitual alcohol seeking. I'll next use the model to compare and contrast changes in the brain and in behavior that occur as a consequence of different types of alcohol selfadministration.

Yury Núñez (Mayfield Lab), Rutgers U. - Small regulatory nucleic acids known as microRNAs (miRNAs), and their apparent combinatorial functioning, are responsible for important changes in gene expression that take place in specific regions of the brains of human alcoholics. I conduct miRNA expression profiling studies in mice and develop methods to efficiently deliver miRNAs or corresponding anti-miRNAs into the mouse brain. By changing miRNA expression levels in vivo, we can assess an interesting battery of miRNAs that could potentially alter the drinking behavior. These studies will help decipher and manipulate the underlying biological phenomena in a genetically amenable animal model. We hope to discover and validate miRNA signatures that could serve as biomarkers and/or therapeutic targets of alcoholism and related complex disorders.

Luisa Scott (Aldrich Lab), U. Rochester - Studies indicate that the large conductance calciumactivated potassium (BK) channel is a target of ethanol. I hope to delineate how the BK channel contributes to ethanol's actions and develop BK channel-targeted pharmaceuticals for the treatment of alcohol abuse by identifying small peptides that alter behavioral sensitivity to ethanol through specific actions at the BK channel. I use phage display to identify peptides for their abilities to bind to a particular target specifically, then validate function of selected peptides in behavioral studies using worms. Finally, I'll test the effects of these peptides on the gating of BK channels expressed in a heterologous system.

HONORS & AWARDS



Richard Aldrich, Professor and Chair of the Section of Neurobiology and Karl Folkers Chair in Interdisciplinary Biomedical Research II (above), became the 52nd President of the Biophysical Society on March 7, 2011. Officers are elected by the membership, which exceeds 9,000.

The Association of Korean Neuroscientists awarded **Chang Hoon Lee** (Harris Lab) an Outstanding Research Award at its annual meeting in San Diego, California, on November 15, 2010. The award recognizes outstanding research accomplishments by students and postdoctoral trainees.

Postdoctoral Fellow **Giorgio Gorini** (Mayfield Lab) received a \$1,120 travel award to attend the 23rd Biennial Meeting of the International Society of Neurochemistry in Athens, Greece, Aug. 28-Sept. 1.

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Our Newletter Gets a Name

Proclivitas is Latin for tendency, predisposition, proneness, all of which are components of addiction.

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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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) isbra.com

(Publications continued next page.)

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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.

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