

2500 Speedway, A4800

MBB 1.124

Austin, Texas 78712

USA

Tel: 512-232-2520

Fax: 512-232-2525

utexas.edu/research/wcaar/

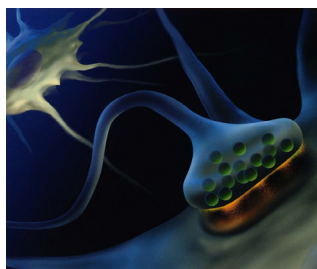
Proclivitas

Spring/Summer 2015

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):

Mendy Black,
Dr. Adron Harris,
Jill Benavidez,
Laura Ferguson, and
Dr. Yuri Blednov

Volume 14, Issue 1

1

Repurposing Existing Drugs to Treat Addiction

Development of drugs to treat human disease is costly, requiring decades of effort and millions in research funding. To optimize this process, scientists are turning to more efficient drug discovery methods, such as testing the potential of drugs already approved by the U.S. Federal Drug Administration to address alternative medical conditions. Researchers in the labs of **R. Adron Harris**, director of the Waggoner Center, and **Hitoshi Morikawa**, associate professor of neuroscience, recently published papers studying the efficacy of diabetes, hyperlipidemia, and hypertension medications in treating addiction.

The drugs tested in the Harris study, including pioglitazone, tesaglitazar, bezafibrate, and fenofibrate, are peroxisome proliferator-activator receptor (PPAR) agonists, which activate PPARs to regulate glucose (diabetes) or lipid (hyperlipidemia) homeostasis. Each drug targets distinct PPAR isoforms (α , γ , and/or δ). Harris and colleagues found that two of the drugs, fenofibrate, which activates PPAR α , and pioglitazone, which stimulates PPAR γ , reduced alcohol consumption in behavioral experiments of mice predisposed to high alcohol intake. Working with investigators

from the Collaborative Study on the Genetics of Alcoholism, they analyzed genomewide association data of human alcoholics to identify genes that code for the different PPAR isoforms. Specific variants of the genes coding for PPAR α and PPAR γ were found in human models of alcohol dependence and withdrawal.

Harris said this “is the first study to combine human genetic studies of alcoholism with animal models of alcohol consumption to show a connection between PPARs and drugs acting on those receptors with alcohol abuse.” This overlapping evidence underscores the potential of PPAR agonists as possible addiction treatments.

These results were published in the journal *Alcoholism: Clinical & Experimental Research*. Other Waggoner Center authors include research scientist **Yuri Blednov**, graduate student **Laura Ferguson** and research associates **Jill Benavidez** and **Mendy Black**.

The Morikawa study, largely conducted by former postdoctoral fellow **Mickaël De-goulet**, focused on disrupting the memories associated with drug-related sensory cues that cause recovering cocaine addicts or alcoholics

Repurposing Drugs (continued)



Claire Stelly and Dr. Hitoshi Morikawa

to relapse. Drug-related cues can be external, like associations with people or places, or internal, such as physiological reactions to the drug. The association of these cues with the effect of addictive drugs in the brain will be learned.

Increased excitatory transmission at specific brain synapses is thought to underlie the learning of drug-associated cues. Degoulet and colleagues found that L-type calcium channels, proteins occurring in cardiac, blood vessel, and neuronal cells, are critical not only for causing but also for maintaining this increased transmission. Administration of the high blood-pressure medication isradipine inhibited these proteins in the brain, which not only blocked the increase in transmission but also promoted reversal of the increased transmission.

In behavioral experiments, rats learned to associate cocaine with a color-coded room and were then given a choice between rooms with and without the drug. After training, they expressed preference for the room with the cocaine. When researchers administered isradipine to cocaine-addicted rats, they soon no longer preferred the room associated with the drug. This effect persisted even when rats were re-exposed to cocaine. In a different experiment, drug-naïve rats receiving a dose of isradipine prior to cue-reward training never learned to associate cocaine with a specific room. These results suggest that isradipine might erase established cue-driven memories.

Graduate student **Claire Stelly** and former postdoctoral fellow **Kee-Chan Ahn** also contributed to the paper, which was published in the journal *Molecular Psychiatry*.

These two studies illustrate the promise of testing and repurposing existing FDA-approved drugs to treat addiction craving and relapse. Combining data from human and animal models, Waggoner Center researchers eventually hope to partner with psychiatrists to conduct clinical trials of the most promising agents.

HONORS & AWARDS

Adam Gordon (Marinelli Lab) and **Matthew Pomrenze** (Messing Lab) received prestigious Graduate Research Fellowships from the National Science Foundation, announced March 31, 2015. The awards are given to early-stage graduate students who demonstrate potential for significant achievements in science and engineering. Out of 16,500 applicants, 2,000 individuals received fellowships, representing a diverse group of scientific disciplines nationwide. The fellowship provides each recipient three years of financial support within a five-year period (\$34,000 annual stipend and \$12,000 cost-of-education allowance).

Gabrielle Zuniga (Pierce-Shimomura Lab) is a 2015 Dean's Honored Graduate in the College of Natural Sciences, graduating in May with an Honors Degree in Biology as a member of the Dean's Scholars and Polymathic Scholars Honors Programs. Honorees represent less than one percent of the college's graduating class. The dean recognized Zuniga for her outstanding

academic record and undergraduate research work in neurogenetics.

The College of Natural Sciences honored **Kimberly Raab-Graham** with a 2015 Teaching Excellence Award and **Jon Pierce-Shimomura** with the 2015 Outreach Excellence Award. The 84th Texas Legislature also commended Pierce-Shimomura and The University of Texas Informal Classes for "a program that enriches the lives of adults with intellectual and developmental disabilities."

Ketan Marballi (Ponomarev Lab) received a Junior Investigator Award to travel to the annual Research Society on Alcohol meeting, held June 20-24, 2015, in San Antonio, TX.

Kelly Jameson (Harris Lab) won a \$500 Award for Excellence in Neuroscience Research at the 2015 Undergraduate Research Forum. The event, sponsored by the College of Natural Sciences, hosted 250 participants. Jameson's prize was one of almost two-dozen awarded.

NEWS

Chancellor William H. McRaven appointed former Provost and Executive Vice President **Steven Leslie** to serve as executive vice chancellor for academic affairs of The University of Texas System, becoming the System's chief academic leader. As the System welcomes two new medical schools to academic campuses, the Dell Medical School at UT Austin and the School of Medicine at UT Rio Grande Valley, Leslie will use his prior academic and medical field experience to promote and foster innovative research collaborations.

Paul J. Kenny, professor and chair of pharmacology and systems therapeutics at the Icahn School of Medicine at Mount Sinai, was the featured speaker at the third annual Waggoner Center Advance on March 27, 2015, at the UT Austin alumni center. Kenny studies the neurobiological mechanisms of drug addiction and spoke about the possible role of microRNAs, which regulate gene expression, in mediating vulnerability to cocaine addiction.

PUBLICATIONS

Bajo M, Herman MA, Varodayan FP, Oleata CS, Madamba SG, **Harris RA**, Blednov YA, Roberto M (2015) Role of the IL-1 receptor antagonist in ethanol-induced regulation of GABAergic transmission in the central amygdala. *Brain Behav Immun* 45:189-197.

Blednov YA, Benavidez JM, Black M, Leiter CR, Osterndorff-Kahanek E, **Harris RA** (2015) Glycine receptors containing alpha2 or alpha3 subunits regulate specific ethanol-mediated behaviors. *J Pharmacol Exp Ther* 353:181-191.

Blednov YA, Benavidez JM, Black M, Mayfield J, **Harris RA** (2015) Role of interleukin-1 receptor signaling in the behavioral effects of ethanol and benzodiazepines. *Neuropharmacology* 95:309-320.

Davis SJ, Scott LL, Ordemann G, Philpo A, **Pierce-Shimomura JT** (2015) Putative calcium-binding domains of the *Caenorhabditis elegans* BK channel are dispensable for intoxication and ethanol activation. *Genes Brain Behav* advance online publication, 26 June 2015; doi: 10.1111/gbb.12229.

Degoulet M, Stelly CE, Ahn KC, **Morikawa H** (2015) L-type Ca²⁺ channel blockade with antihypertensive medication disrupts VTA synaptic plasticity and drug-associated contextual memory. *Mol Psychiatry* advance online publication, 23 June 2015; doi:10.1038/mp.2015.84.

Doherty JM, **Gonzales RA** (2015) Operant self-administration of sweetened ethanol and time course of blood ethanol levels in adolescent and adult male Long-Evans rats. *Alcohol Clin Exp Res* 39:485-495.

Farley NM, **Mihic SJ** (2015) Allosteric modulation of the glycine receptor activated by agonists differing in efficacy. *Brain Res* 1606:95-101.

Farris SP, **Harris RA**, Ponomarev I (2015) Epigenetic modulation of brain gene networks for cocaine and alcohol abuse. *Front Neurosci*. May 20;9:176. doi: 10.3389/fnins.2015.00176.

Farris SP, Pietrzykowski AZ, Miles MF, O'Brien MA, Sanna PP, Zakhari S, **Mayfield RD**, **Harris RA** (2015) Applying the new genomics to alcohol dependence. *Alcohol* advance online publication, 28 March 2015; doi: 10.1016/j.alcohol.2015.03.001.

Harden KP, Carlson MD, Kretsch N, Corbin WR, **Fromme K** (2015) Childhood sexual abuse and impulsive personality traits: mixed evidence for moderation by genotype. *J Res Pers* 55:30-40.

Hines KE, Bankston JR, **Aldrich RW** (2015) Analyzing single-molecule time series via nonparametric Bayesian inference. *Biophys J* 108:540-556.

Horani S, Stater EP, Corringer PJ, Trudell JR, **Harris RA**, Howard RJ (2015) Ethanol modulation is quantitatively determined by the transmembrane domain of human $\alpha 1$ glycine receptors. *Alcohol Clin Exp Res* 39:962-968.

Kumar V, Weng YC, Geldenhuys WJ, Wang D, Han X, **Messing RO**, Chou WH (2015) Generation and characterization of ATP analog-specific protein kinase C δ . *J Biol Chem* 290:1936-1951.

Lee AM, Wu D-F, Dadgar J, Wang D, McMahon T, **Messing RO** (2015) Protein kinase C epsilon phosphorylates $\alpha_4\beta_2$ nicotinic acetylcholine receptors and promotes recovery from desensitization. *Br J Pharmacol* advance online publication, 23 June 2015; doi: 10.1111/bph.13228.

Marino EN, **Fromme K** (2015) Alcohol-induced blackouts and maternal family history of problematic alcohol use. *Addict Behav* 45:201-206.

Most D, Leiter C, **Blednov YA**, **Harris RA**, **Mayfield RD**. (2015) Synaptic microRNAs Coordinately Regulate Synaptic mRNAs: Perturbation by Chronic Alcohol Consumption. *Neuropsychopharm* advance online publication, 24 Jun 2015; doi: 10.1038/npp.2015.179.

Osterndorff-Kahanek EA, Becker HC, Lopez MF, Farris SP, Tiwari GR, Nunez YO, **Harris RA**, **Mayfield RD** (2015) Chronic ethanol exposure produces time- and brain region-dependent changes in gene coexpression networks. *PLoS One* 10:e0121522.

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

or call: 512-471-3299

or contact:

College of Natural Sciences
Dean's Office

The University of Texas
at Austin

120 Inner Campus Drive
Stop G2500
Austin, TX 78712

Useful Websites

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

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

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

Research Society on Alco-
holism (RSA), rsoa.org

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

(Publications continued
next page.)

THE UNIVERSITY OF TEXAS AT AUSTIN

Waggoner Center

for Alcohol & Addiction Research

utexas.edu/research/wcaar/

2500 Speedway, A4800

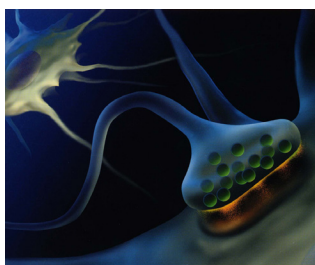
MBB 1.124

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 the university.

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.

Associate Director:

Robert O. Messing, M.D.

Writing/Editing/Design:

Marsha Berkman, Jody Mayfield

Thanks to: Hitoshi Morikawa, Laura Ferguson, Claire Stelly

PUBLICATIONS (continued)

Polioudakis D, Abell NS, **Iyer VR** (2015) MiR-191 regulates primary human fibroblast proliferation and directly targets multiple oncogenes. *PLoS One* 10:e0126535.

Polioudakis D, Abell NS, **Iyer VR** (2015) miR-503 represses human cell proliferation and directly targets the oncogene DDHD2 by non-canonical target pairing. *BMC Genomics* 16:40.

Reno JM, Thakore N, **Gonzales R, Schallert T**, Bell RL, Maddox WT, **Duvauchelle CL** (2015) Alcohol-preferring P rats emit spontaneous 22-28 kHz ultrasonic vocalizations that are altered by acute and chronic alcohol experience. *Alcohol Clin Exp Res* 39:843-852.

Renteria R, Jeanes ZM, **Morrisett RA** (2014) Ethanol attenuation of long-term depression in the nucleus accumbens can be overcome by activation of TRPV1 receptors. *Alcohol Clin Exp Res* 38:2763-2769.

Schuckit MA, Smith TL, Kalmijn J, Skidmore J, Clausen P, Shafir A, Saunders G, Bystritsky H, **Fromme K** (2015) The impact of focusing a program to prevent heavier drinking on a pre-existing phenotype, the low level of response to alcohol. *Alcohol Clin Exp Res* 39:308-316.

Sosanya NM, Cacheaux LP, Workman ER, Niere F, Perrone-Bizzozero NI, **Raab-Graham KF** (2015) Mammalian Target of Rapamycin (mTOR) Tagging Promotes Dendritic Branch Variability through the Capture of Ca²⁺/calmodulin-dependent protein kinase II α (CaMKII α) mRNAs by the RNA-binding Protein HuD. *J Biol Chem* 290:16357-16371.

Vena AA, **Gonzales RA** (2015) Temporal profiles dissociate regional extracellular ethanol versus dopamine concentrations. *ACS Chem Neurosci* 6:37-47.

Workman ER, Haddick PC, Bush K, Dilly GA, Niere F, Zemelman BV, **Raab-Graham KF** (2015) Rapid antidepressants stimulate the decoupling of GABA(B) receptors from GIRK/Kir3 channels through increased protein stability of 14-3-3 η . *Mol Psychiatry* 20:298-310.