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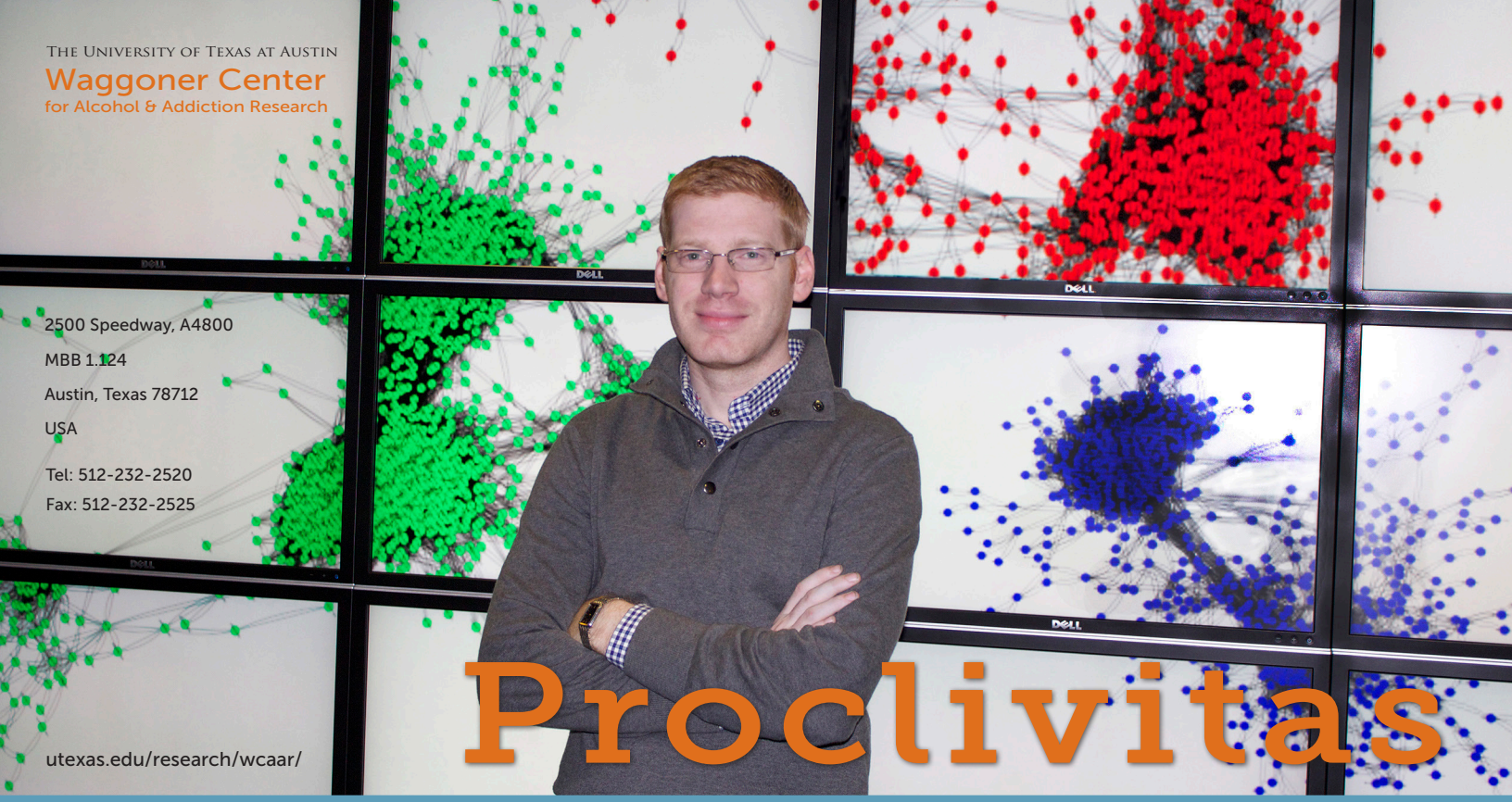
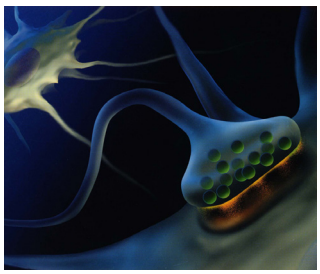


Proclivitas

Fall/Winter 2014 Waggoner Center for Alcohol & Addiction Research Newsletter

Our Mission

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



Above:

Dr. Sean Farris photographed in the Vislab on the UT Austin campus. The background image displays gene networks from alcoholic tissue.

Volume 13, Issue 2

Alcohol Consumption Networks in the Brain

Researchers at The University of Texas at Austin have found convergent evidence of gene networks related to alcohol consumption in human alcoholics. These networks of coordinately expressed gene sets with common biological functions provide a systems-level model of alcohol dependence.

Postdoctoral Fellow **Sean P. Farris**, Director **R. Adron Harris**, and Research Scientist **R. Dayne Mayfield** of the Waggoner Center, with Bioinformatician **Dhivya Arasappan** of the Center for Systems and Synthetic Biology, and Director **Scott Hunicke-Smith** of the Genomic Sequencing and Analysis Facility, recently published the results of their study in the journal *Molecular Psychiatry*.

"We hope our model can serve as a type of Wikipedia of alcohol dependence," said Farris. "It could be used as a reference for future studies, such as exploration of specific drug targets in the network or identification of new gene isoforms unique to humans."

Individuals contain genes encoding thousands of traits, such as physical attributes and certain types of behaviors or disease. But only some of the genes will become activated or expressed as a product of our inherited DNA and environmental stimuli. Gene expression results in phenotypes – a composite of traits such as physical appearance or a disease state like muscular dystrophy or cancer. The purpose of this study was to arrive at a comprehensive picture of the gene sets driving the phenotype of alcohol dependence.

To reach this goal, Farris et al. compared post mortem, prefrontal cortex brain tissue in alcoholic and non-alcoholic groups, assessing global differences between the two groups and then defining the distinguishing characteristics of the alcoholic group.

At a global level, gene connectivity, representing fully functional biological processes, was weaker in the alcoholic group. This dysregulation of normal biological function is a hallmark of alcohol dependence.

(Feature continued next page.)

Alcohol Networks (continued)

To understand the specific gene sets associated with lifetime alcohol consumption, they compared transciptome patterns in the alcoholic and control groups. The transcriptome is the set of RNA molecules present in the tissue, which indicates the genes being expressed. The researchers identified coordinately regulated genes and organized similar gene networks into separate modules to help conceptualize how they operate as part of a whole. Creating a modular system facilitates association between specific traits of alcohol dependence and gene expression profiles. The researchers identified 38 gene modules in the alcoholic group and 32 such modules in the control group.

Gene modules fell into four quartiles of relevance to alcohol dependence. Those in the upper quartile showed the strongest relevance. These modules contain genes governing biological processes such as synaptic plasticity, ion channel function, neurotransmitter transporters, and intracellular signaling. What distinguished the alcoholic group from the control group was higher intermodular correlation to lifetime alcohol consumption among gene modules in the upper quartile. This strong interconnectedness of gene networks linked to alcohol dependence was absent in the control tissue. The alcohol consumption networks in the alcoholic tissue suggest subtle transcriptome reorganization in response to alcohol dependence. They may also indicate an allostatic mechanism – a physiological process to regain homeostasis - to overcome changes associated with alcohol dependence.

Farris and his colleagues are now building a data visualization model of their results. A color-coded wheel representing the various gene modules will correspond to a color-coded anatomical model so that biological functions tied to specific gene modules can be seen more readily.

This study was funded by the National Institute on Alcohol Abuse and Alcoholism through the American Recovery and Reinvestment Act, also known as the Stimulus Act (grant no. RC2 AA019382). Mayfield, who served as the grant's principal investigator, was one of the competitive funding source's few recipients. "The work represents the culmination of collaborative and integrative efforts across campus involving a team of highly skilled and devoted researchers and state-of-the-art resources," said Mayfield. "The findings advance the study of genomic profiling in human alcoholics and demonstrate how unique approaches and applications can break down the complexities of alcohol dependence into relevant biological networks."

RECENT FUNDING NEWS

Principal Investigator: **Dr. Nigel Atkinson** (Neuroscience)
Project Title: "Epigenetic Dissection of Functional Ethanol Tolerance and Dependence"
Award Total: $1,689,075 (five years), Sponsor: National Institute on Alcohol Abuse & Alcoholism

Principal Investigator: **Dr. Rueben A. Gonzales** (Pharmacology & Toxicology)
Co-Principal Investigator: **Dr. Richard Morrisett** (Pharmacology & Toxicology)
Project Title: "Mu Receptors and Ethanol/Dopamine Interactions"
Award Total: $1,056,429 (four years), Sponsor: National Institute on Alcohol Abuse & Alcoholism

Principal Investigator: **Dr. Daniel S. McGehee** (Neuroscience, University of Chicago)
Co-Principal Investigator: **Dr. Michela Marinelli** (Pharmacology & Toxicology)
Project Title: "Cellular Basis of Nicotine Induced Aversion"
Award Total: $1,898,710 (five years), Sponsor: National Institute on Drug Addiction

Principal Investigator: **Dr. Greg Sutherland** (Sydney Medical School, The University of Sydney)
Co-Principal Investigator: **Dr. R. Dayne Mayfield** (Waggoner Center)
Project Title: "The Microglial Transcriptome in Health and Disease"
Award Total: $80,000 (two years), Sponsor: Sydney Medical School Foundation

HONORS & AWARDS

Dr. Rueben A. Gonzales was elected to a three-year term as an officer of the Research Society on Alcoholism, beginning June 2014. He currently serves as vice president. He'll serve as president and past-president during the subsequent years of his tenure.

Graduate student **John Valenta** (Gonzales Lab) was one of two student winners of the Enoch Gordis Research Recognition Award at the 37th annual RSA meeting held June 21-25, 2014, in Bellevue, WA. His poster was titled "The effect of chronic intracerebroventricular (ICV) monocyte chemotactic protein-1 (MCP-1) on ethanol self-administration."

Shannon Zandy, a graduate student in the Gonzales Lab, received a poster award at the 15th Annual Monitoring Molecules in Neuroscience Conference for her work titled "Analysis of *in vivo* extracellular GABA in midbrain via quantitative microdialysis using high performance liquid chromatography with electrochemical detection." The international conference took place August 3-7, 2014, in Los Angeles, CA.

Doctoral Degrees Awarded

Scott Davis, Ph.D. (Pierce-Shimomura Lab), Jun. 26, 2014 "A Critical Residue on the BK Channel required for Ethanol Intoxication"

Joshua Russell, Ph.D. (Pierce-Shimomura Lab), Aug. 7, 2014 "Uncovering the Neuromolecular Basis for Hygrotaxis in *Caenorhabditis elegans*"

PUBLICATIONS

Blednov YA, Benavidez JM, Black M, Ferguson LB, Schoenhard GL, Goate AM, Edenberg HJ, Wetherill L, Hesselbrock V, Foroud T, **Harris RA** (2014) Peroxisome proliferator-activated receptors α and γ are linked with alcohol consumption in mice and withdrawal and dependence in humans. *Alcohol Clin Exp Res*, in press.

Cui C, Shurtleff D, **Harris RA** (2014) Neuroimmune mechanisms of alcohol and drug addiction. *Int Rev Neurobiol* 118:1-12.

Davis SJ, Scott LL, Hu K, **Pierce-Shimomura JT** (2014) Conserved single residue in the BK potassium channel required for activation by alcohol and intoxication in C. elegans. *J Neurosci* 34:9562-9573.

Dembrow N, **Johnston D** (2014) Subcircuit-specific neuromodulation in the prefrontal cortex. *Front Neural Circuits* 8:54.

Farris SP, **Mayfield RD** (2014) RNA-Seq reveals novel transcriptional reorganization in human alcoholic brain. *Int Rev Neurobiol* 116:275-300.

Farris SP, Arasappan D, Hunicke-Smith S, **Harris RA, Mayfield RD** (2014) Transcriptome organization for chronic alcohol abuse in human brain. *Mol Psychiatry* advance online publication, 2 Dec 2014; doi:10.1038/mp.2014.159.

Ferguson LB, Most D, **Blednov YA**, **Harris RA** (2014) PPAR agonists regulate brain gene expression: Relationship to their effects on ethanol consumption. *Neuropharmacology* 86:397-407.

Gorini G, **Harris RA, Mayfield RD** (2014) Proteomic approaches and identification of novel therapeutic targets for alcoholism. *Neuropsychopharmacology* 39:104-130.

Halling DB, Kenrick SA, Riggs AF, **Aldrich RW** (2014) Calcium-dependent stoichiometries of the KCa2.2 (SK) intracellular domain/calmodulin complex in solution. *J Gen Physiol* 143:231-252.

Jeanes ZM, Buske TR, **Morrisett RA** (2014) Cell type-specific synaptic encoding of ethanol exposure in the nucleus accumbens shell. *Neuroscience* 277:184-195.

Lee AM, Zou ME, Lim JP, Stecher J, McMahon T, **Messing RO** (2014) Deletion of Prkcz increases intermittent ethanol consumption in mice. *Alcohol Clin Exp Res* 38:170-178.

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Lovely CB, **Eberhart JK** (2014) Commentary: catching a conserved mechanism of ethanol teratogenicity. *Alcohol Clin Exp Res* 38:2160-2163.

Lovely CB, Nobles RD, **Eberhart JK** (2014) Developmental age strengthens barriers to ethanol accumulation in zebrafish. *Alcohol* 48:595-602.

Maiya RP, **Messing RO** (2014) Peripheral systems: neuropathy. *Handb Clin Neurol* 125:513-525.

Mangieri RA, Cofresi RU, **Gonzales RA** (2014) Ethanol exposure interacts with training conditions to influence behavioral adaptation to a negative instrumental contingency. *Front Behav Neurosci* 8:220.

Marinelli M, McCutcheon JE (2014) Heterogeneity of dopamine neuron activity across traits and states. *Neuroscience* 282C:176-197.

McCarthy N, **Eberhart JK** (2014) Gene-ethanol interactions underlying fetal alcohol spectrum disorders. *Cell Mol Life Sci* 71:2699-2706.

McGurk PD, Lovely CB, **Eberhart JK** (2014) Analyzing craniofacial morphogenesis in zebrafish using 4D confocal microscopy. *J Vis Exp* 83:e51190.

(Publications continued next page.)

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 contact:
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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 Alcoholism (RSA), rsoa.org

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

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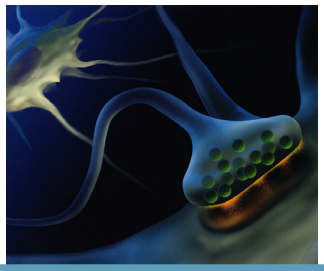

The Waggoner Center for Alcohol and Addiction Research was established in 1999 at The University of Texas at Austin. The center was made possible by a donation from M. June and J. Virgil Waggoner and matching funds from the university. The mission of the center is to create a premier research center for alcohol and addiction research, thereby developing solutions for the prevention and cure of these diseases.

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R. Adron Harris, Ph.D.

Associate Director:
Robert O. Messing, M.D.

Editing/Design:
Marsha Berkman, Jody Mayfield

Many thanks to: Sean Farris and Dayne Mayfield

PUBLICATIONS (continued)

Most D, Ferguson L, **Blednov YA, Mayfield RD, Harris RA** (2014) The synaptoneurosome transcriptome: a model for profiling the molecular effects of alcohol. *Pharmacogenomics J* advance online publication, 19 Aug 2014; doi: 10.1038/tpj.2014.43.

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Park D, Morris AR, Battenhouse A, **Iyer VR** (2014) Simultaneous mapping of transcript ends at single-nucleotide resolution and identification of widespread promoter-associated non-coding RNA governed by TATA elements. *Nucleic Acids Res* 42**:**3736-3749.

Robinson G, Most D, Ferguson LB, Mayfield J, **Harris RA, Blednov YA** (2014) Neuroimmune pathways in alcohol consumption: evidence from behavioral and genetic studies in rodents and humans. *Int Rev Neurobiol* 118**:**13-39.

Sosanya NM, Brager DH, Wolfe S, Niere F, **Raab-Graham KF** (2014) Rapamycin reveals an mTOR-independent repression of Kv1.1 expression during epileptogenesis. *Neurobiol Dis* 73C**:**96-105.

Swartz ME, Wells MB, Griffin M, McCarthy N, Lovely CB, McGurk P, Rozacky J, **Eberhart JK** (2014) A screen of zebrafish mutants identifies ethanol-sensitive genetic loci. *Alcohol Clin Exp Res* 38**:**694-703.