

NIAAA Renews PARC P60 2006-2010

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) awards the Portland Alcohol Research Center \$9.0 million over next five years

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PORTLAND ALCOHOL RESEARCH CENTER

VA Medical Center, R&D 12
Portland OR 97239 USA
Tel: 503.220.8262 x56653
Fax: 503.721.1029
E-mail:
rutledgm@ohsu.edu
Website:
www.ohsu.edu/parc



Portland VA
Medical Center



Oregon Health & Science University

The NIAAA has recently awarded us a third 5 years of support. As the research and other mutually supportive interactions of Portland investigators have matured, we have developed a group that is recognized for its unique combination of expertise in the application of genetic animal

models to assess the mechanisms of alcohol neuroadaptation,

and to discover genes associated with alcohol abuse and alcoholism. We have come to call our approach behavioral genomics, by which we mean that as we discover genes of importance, we will make it a priority to determine their influence on the integrated, behavioral adaptations of the whole animal. Over the 10 years of the PARC's existence, we have begun to focus on two specific hypotheses. The first is the intriguing idea that withdrawal and drinking may be influenced by some of the same genes. Across many different studies and genotypes, it has proven to be the case that high-withdrawal genotypes are genetically predisposed to drink less than low-withdrawal genotypes. PARC projects headed by John Belknap, Kari Buck, and Bob Hitzemann are pursuing genes underlying this relationship. The second emergent hypothesis is that high impulsivity is a significant genetic risk factor for high alcohol drinking. There is of course much epidemiological and genetic evidence for this in the human literature on alcoholism and other addictive drugs. Projects headed by two investigators new to the PARC, Suzanne Mitchell and Judy Cameron, are beginning to test this idea in mice and non-human primates, respectively.

One new aspect to our gene finding efforts has been the extension into large-scale (genome wide) studies of gene expression using microarray analyses. As a necessary adjunct to these studies, we have developed a substantial biostatistical and bioinformatics effort devoted to relating the information we gather on the activity of thousands of genes to information available in the many databases of genomic information. While our efforts remain focused on the mouse, the individual rhesus being studied at the Oregon National Primate Research Center by Judy Cameron are all genotyped, and in the coming years, we

hope to translate mouse genomics findings not only into human genetics but also non-human primate genetics. Finally, the bioinformatics group is allowing us to implement sophisticated birth-to-death data management systems for the many mouse colonies we have devel-

oped for PARC and other studies. The Microarray, Bioinformatics and Biostatistics Core

efforts, headed by John Belknap, Shannon McWeeney, and Bob Hitzemann are therefore being coordinated with the Animal and Dependence Core efforts, managed by Tamara Phillips and Pamela Metten.

The other new aspect to this iteration of the PARC is that we have been designated a P60 Comprehensive Research Center by NIAAA. This recognizes the long-standing efforts of Mark Rutledge-Gorman to bring the science in the PARC to the lay public in various venues. He also oversees the many programs that bring high school and undergraduate students into PARC laboratories, and he works with a local middle school teacher to bring curriculum developed by PARC and the NIAAA into local classrooms.

We are looking forward to the "new PARC," and are committed to bringing its scientific goals to fruition while we develop new investigators at every level, from faculty through middle school.

- John C. Crabbe, Ph.D.
Center Director

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The mission of the Center is to identify genes and explore mechanisms underlying neuroadaptation to alcohol.

PARC News is published by the Portland Alcohol Research Center to report on the work of the Center and to advance research on alcoholism.

Center Director: John C. Crabbe, Ph.D.
Editor: Mark Rutledge-Gorman, Psy.D.
Assoc. Editor: Suzanne Mitchell, Ph.D.
Comments: rutledgm@ohsu.edu

Center Components



Component 1: Administrative Core.

Center Director: John Crabbe (pictured left) Scientific Director: Robert Hitzemann
The Administrative Core coordinates the activities of the Scientific Support Cores (Components #2-4), the Research Components (#5-10) and the Education and Outreach Component (#11). Scientific oversight is provided by an external Scientific Advisory Board, and by an internal Executive Committee made up of component PIs.



Component 2: Animal and Dependence Core.

Director: Tamara Phillips (pictured left) Co-Director: Pamela Metten
The Animal and Dependence Core (Component 2) serves all Center projects that require the use of mice. The objective of this Core is to streamline animal production, distribution and testing of key phenotypes for PARC-related projects. The Dependence Division of the Core continues to optimize procedures for inducing dependence. The Core also maintains data on animals produced by the Core to share with the PARC Microarray, Bioinformatics and Biostatistics Core (Component 4) to facilitate data analyses. Finally, the Core maintains previously created and new genetic animal models that exist nowhere else and will make them available to investigators as requested.



Component 3: Molecular Genetics Support Core.

Director: Kari Buck (pictured left) Co-Director: Renee Shirley
The Molecular Genetics Support Core provides services to all Research Components and Pilot Projects requiring molecular biological and genetic assays. In the past 5 years, we identified chromosomal regions (called quantitative trait loci, QTLs) that contain some of the genes involved in behavioral responses to ethanol including preference and withdrawal. Several QTLs have been mapped to 1-2 Mb. We identified the quantitative trait gene (QTG) for a withdrawal QTL on chromosome 4 as *Mpdz*. In the current 5 years of support, complementary strategies will emphasize fine mapping of new QTLs, identification and definitive proof of QTGs for preference, withdrawal, and correlated responses to ethanol.



Component 4: Microarray, Bioinformatics, and Biostatistics Core.

Director: John Belknap (pictured left) Co-Dir: Shannon McWeeney, Christina Harrington, Robert Hitzemann. Core Component 4 carries out all QTL (quantitative trait locus) and microarray analyses, QTL/microarray integration, and informatics, computational and statistical support necessary for the center. The largest change in the renewal compared to our present Component is the much increased support needed for the microarray gene expression studies and their integration with QTL analyses. Microarrays allow the screening of gene expression of tens of thousands of genes for their relationship to key genotypes known to differ for alcohol-relevant traits. QTL analyses allow the dissection of continuous variation of a trait into component genetic loci, and to map them to chromosomal regions.

Research Component 5: Genetic Analysis of Gene Expression: Alcohol Acute Withdrawal Severity and Alcohol Preference Drinking.

PI: John Belknap (pictured, see Component 4) Co-Is: John Crabbe, Robert Hitzemann, Pamela Metten
Prior work in the PARC has established that two alcohol traits, acute withdrawal severity and preference drinking, are genetically correlated in several C57BL/6J (B6) x DBA/2J (D2) populations, which strongly suggests the presence of common Quantitative Trait Loci (QTLs) influencing these two traits, and thus also common genetically-mediated mechanisms. During this period of support, we will use selective breeding strategies to greatly increase the frequency of extreme phenotypes and associated genotypes, and hence greatly facilitate detection of QTLs influencing either trait separately as well as both traits jointly.

Center Components, cont.

Research Component 6: Characterization of Ethanol Response QTLs on Chromosome 11.

PI: Kari Buck (pictured, see Component 3) Co-I: Robert Hitzemann

This research component examines genes on Quantitative Trait Loci (QTLs) on chromosome 11 for expression to determine where and when they are expressed. A strength of this project is that we have progressed to identify the GABA_A receptor $\alpha 2$ subunit gene (*Gabrg2*) as a promising candidate gene. Our work will progress toward identification of specific genes on chromosome 11 that confer sensitivity to, or protection from, ethanol withdrawal. This will set the stage for future translational and mechanistic studies.

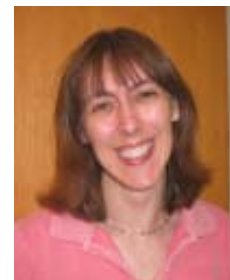
Research Component 7: High Throughput Strategy for Ethanol Quantitative Trait Genes (QTGs).

PI: Robert Hitzemann (pictured right) Co-Is: John Belknap, Kari Buck, Tamara Phillips
Research component 7 uses a high throughput strategy for the detection of quantitative trait genes (QTGs) associated with ethanol preference. The research strategy integrates several different experimental approaches; these include multiple cross mapping, fine mapping in heterogenous stock animals, the integration of QTL analysis and functional genomics, the use of short term selective breeding to confirm QTLs and follow gene segregation and QTL confirmation in transgenic mice.



Research Component 8: Using Genetic Models to Examine Variation in Impulsivity and Links with Alcoholism.

PI: Suzanne Mitchell (pictured right) Co-Is: Chris Cunningham, Tamara Phillips
High levels of impulsivity may predict initial experimentation with alcohol and responses to alcohol that are associated with its continued use. Neuroadaptations to alcohol also may acutely or chronically increase impulsive decision-making. This project examines these associations in inbred strains of mice by assessing the genetic contribution to variations in impulsivity and the extent to which these variations exhibit genetic correlations with ethanol-related traits.



Research Component 9: Genetics of Alcohol-Associated Traits in Monkeys

PI: Judy Cameron (pictured right) Co-Is: John Crabbe, Chris Cunningham, T. Hobbs, D. Williamson
This project seeks to identify genes associated with individual differences in behavioral and physiological measures that have been identified as indicators of risk of alcoholism in humans or of an increased propensity to consume alcohol in animal species. We capitalize on an ongoing linkage study in young rhesus monkeys designed to identify the genes underlying anxious and depressive behaviors (behaviors which themselves have been linked to increased consumption of alcohol), by screening the same monkeys for additional behavioral and physiological responses.



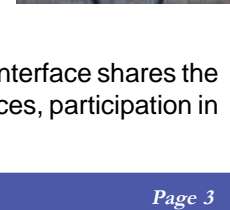
Research Component 10: 2006 Pilot Projects

PI: Amy Eshleman Ethanol Stimulation and the Dopamine Transporter
PI: Deborah Finn Hippocampal Neurosteroids and Ethanol Withdrawal Severity
PI: Matthew Lattal Effects of Ethanol on Extinction Processes
PI: Andrey Ryabinin V1a Receptors, Ethanol Preference and Tolerance.



Education Component 11: Education and Outreach

Director: Mark Rutledge-Gorman (pictured right) Co-Directors: Chris Cunningham, William Cameron
This Component conducts three programs to translate and disseminate alcohol research findings to health care providers, researchers, policymakers and the public. The K-12 program provides students and their teachers with activities and information about alcohol, the brain, and neuroscience. Our Training in Alcohol Research program gives training and laboratory experience in alcohol research to high school, undergraduate, graduate, and post-doctoral students. The Dissemination and Translational Interface shares the findings of the Center through professional and lay publications, the Center's website, scientific conferences, participation in the University's speaker and scientific expert bureau, and media contacts.



National Resources

National Institute on Alcohol Abuse and Alcoholism
Information, research programs, databases, links
www.niaaa.nih.gov

Substance Abuse & Mental Health Services Administration
Information and referral to local treatment in your area
1-800-662-4357
www.samhsa.gov

Regional Resources

Mental Health / A&D
Portland OR and Multnomah Co.
24-hr Crisis and Referral
503-215-7082

Clark Co. WA Crisis Line
24-hr Crisis and Referral
696-9560
1-800-626-8137

State of Oregon
Office of Alcohol & Drug Abuse Programs
503-945-5763
www.oadap.hr.state.or.us

State of Washington
Division of Alcohol & Substance Abuse
1-800-562-1240

PORTLANDALCOHOL
RESEARCHCENTER

VA Medical Center, R&D 12
Portland OR 97201 USA
Tel: 503.220.8262 x56653
Fax: 503.721.1029
E-mail:
rutledgm@ohsu.edu
Website:
www.ohsu.edu/parc



Selected Center Publications

- Kliethermes, C. L. and Crabbe J. C. (2006). **Genetic independence of mouse measures of some aspects of novelty seeking.** *Proceedings of the National Academy of Sciences USA* 103:5018-23.
- Finn, D. A., Douglass, A. D., Beadles-Bohling, A. S., Tanchuck, M. A., Long, S. L., and Crabbe, J. C. (2006). **Selected line difference in sensitivity to a GABAergic neurosteroid during ethanol withdrawal.** *Genes, Brain and Behavior* 5: 53-63.
- Crawshaw, L. I., Wallace, H. L., O'Connor, C. S., Yoda, T., and Crabbe, J. C. (2006). **Tolerance and withdrawal in goldfish exposed to ethanol.** *Physiology and Behavior*. 87:460-8.
- Hood, H. M., Metten, P., Crabbe, J. C., and Buck, K. J. (2006). **Fine mapping of a sedative-hypnotic drug withdrawal locus on mouse chromosome 11.** *Genes, Brain and Behavior* 5: 1-10.
- Mulligan, M. K., Ponomarev, I., Hitzemann, R. J., Belknap, J. K., Tabakoff, B., Harris, R. A., Crabbe, J. C., Blednov, Y. A., Grahame, N. J., Phillips, T. J., Finn, D. A., Hoffman, P. L., Iyer, V. R., Koob, G. F., Bergeson, S. E. (2006). **Toward understanding the genetics of alcohol drinking through transcriptome meta-analysis.** *Proceedings of the National Academy of Sciences USA* 103:6368-73.
- Rhodes, J. S., Ford, M. M., Yu, C. H., Brown, L. L., Finn, D. A., Garland, T., and Crabbe, J. C. (2006). **Mouse inbred strain differences in ethanol drinking to intoxication.** *Genes, Brain and Behavior* OnlineEarly publication date: 13-Feb-2006.
- Lovinger, D. M. and Crabbe, J. C. (2005). **Laboratory models of alcoholism: treatment target identification and insight into mechanisms.** *Nature Neuroscience* 8: 1471-1480.
- Fehr, C., Shirley, R. L., Crabbe, J. C., Belknap, J. K., Buck, K. J., and Phillips, T. J. (2005). **The syntaxin binding protein 1 gene (*Stxbp1*) is a candidate for an ethanol preference drinking locus on mouse chromosome 2.** *Alcoholism: Clinical and Experimental Research* 29: 708-720.
- Weitemier, A. Z., Tsivkovskaia, N. O., and Ryabinin, A. E. (2005). **Urocortin 1 distribution in mouse brain is strain-dependent.** *Neuroscience* 132: 729-740.
- Finn, D. A., Belknap, J. K., Cronise, K., Yoneyama, N., Murillo, A., and Crabbe, J. C. (2005). **A procedure to produce high alcohol intake in mice.** *Psychopharmacology* 178: 471-480.
- Meyer, P. J., Palmer, A. A., McKinnon, C. S., and Phillips, T. J. (2005). **Behavioral sensitization to ethanol is modulated by environmental conditions, but is not associated with cross-sensitization to allopregnanolone or pentobarbital in DBA/2J mice.** *Neuroscience* 131: 263-273

Awards to Center Scientists and Trainees

- Helen Kamens**, 2006 Portland University Club Graduate Student Fellowship, awarded to the outstanding OHSU student for research and educational outreach (Tamara Phillips, mentor); 2006 OHSU School of Medicine Alliance Award for scholarship, leadership, and current and potential contributions to biomedicine and society (awardee becomes OHSU nominee for Fellowship above)
- Christa Helms**, 2006 OHSU Student Council Award, for excellence in for Academics & Service (Suzanne Mitchell, mentor)
- Matthew Ford**, OHSU Alumni Award for best Postdoctoral Paper for a paper published in 2005, Ford MM, Nickel JD, Phillips TJ, Finn DA (2005) Neurosteroid modulators of GABA(A) receptors differentially modulate Ethanol intake patterns in male C57BL/6J mice. *Alcohol Clin Exp Res* 29(9):1630-1640. (Deborah Finn, mentor)
- 2006 Tartar Research Fellowships**: Ethan Beckley (Deborah Finn, mentor), Katie Gilliland (Deborah Finn, mentor), Christina Gremel (Chris Cunningham, mentor), Skyla Herod (Judy Cameron, mentor), Lauren Milner (Kari Buck, mentor)
- Ethan Beckley**, Nancy & Dodd Fischer Scholarship, ARCS Foundation, 2005 (Deborah Finn, mentor)
- Kari Buck**, new VA Merit grant, Genetic Vulnerability to Alcohol Physical Dependence
- William Cameron**, new R25 RR20443-01, Teacher Institute for the Experience of Science
- John Crabbe**, OHSU School of Medicine's 2006 John A. Resko Faculty Research and Mentoring Award for outstanding research and mentoring