

PARC News

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The Newsletter of the Portland Alcohol Research Center

NIAAA Renews Portland Alcohol Research Center 2001-06

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) awards the Center \$8.9 million over the next five years

Director John Crabbe provides perspective on the PARC as well as leadership

The big news is that the Center's funding has been renewed for a second five-year term, effective January 2001. The renewal is gratifying and I've been offered this opportunity to reflect a bit on the Center's course - where we started, and where we're going. ***The PARC remains firmly oriented toward locating identifying and explicating the function of genes affecting risk for, and protection against, alcohol's chronic maladaptive effects on the brain.*** The efforts of our group along these lines started before 1990 and were originally supported with a Program Project Grant before we initially obtained funding as an NIH-supported Research Center in 1995. After 10 years of effort toward this broad goal, we find ourselves in the midst of the genomics revolution, where methods, resources, and potential applications are changing so quickly that our new directions include some we could barely conceive at the beginning.

First, the accomplishments. We've been blessed with an extremely talented group of scientists. Three of our scientists (Tamara Phillips, Deb Finn, and Kari Buck) were recognized by the Research Society on Alcoholism as the Outstanding Young Investigator of the year. Most of our original group is still with us, and we've recruited new investigators into the fold during the past 5 years. ***John Belknap, one key member of our group and my oldest collaborator, has become recognized in the alcohol/substance abuse genetics field for his contributions to the statistical methods for ascertaining gene location in the animal models we use.*** Using his strategies, our group collectively has provided genomic locations for about one half of all the genes thus far mapped in rats or mice for alcohol-related traits.

The past five years have been devoted to fine genetic mapping. We have had the locations for many of these genes in hand since as early as 1997, but the areas of the genome mapped have

been too large to identify the specific genes involved. Recently, Kari Buck and her postdoctoral fellow, Christoph Fehr, have narrowed the genomic location for one gene we are pursuing to a specific region of mouse chromosome 4 that comprises about 600,000 base pairs of DNA. This may sound enormous, but the region harbors only about 30 genes. Kari and Christoph have shown that one of those genes leads mice to experience severe alcohol withdrawal. It is likely that the same gene, or another nearby, also affects withdrawal from a barbiturate. ***Kari and Christoph are an order of magnitude closer to identifying a "risk" gene with certainty than any other group in the world that is chasing genes relevant for substance abuse in animal models***

"...our new directions include some we could barely conceive at the beginning."

What comes next? The gene mapping/gene function studies will continue to progress. OHSU is establishing a functional genomics capacity, which will provide the ability to employ gene expression array technology to determine which genes' functions are affected by chronic alcohol exposure. The University-wide scale will allow us to make effective use of these methods

beyond those that can be realized in our individual investigators' laboratories. ***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.*** We have termed this perspective "behavioral genomics" to distinguish its goals from the pursuit of gene function at the cellular and intracellular level. In another development, the OHSU Advanced Research Imaging Center that is coming on line will someday offer us the opportunity to view brain function & even gene expression *in vivo* using some variant of functional magnetic resonance imaging or magnetic resonance spectroscopy.

Collectively, the PARC has achieved some remarkable accomplishments. We continue to take advantage of new developments, and look forward to the challenges and opportunities which will be emerging at the time of our next renewal.



John Crabbe

Inside This Issue

Selected Publications.....	2
Education & Outreach.....	2, 4
Awards.....	3
Research Seminars.....	3

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Portland VA
Medical Center



Oregon Health & Science University

Education and Outreach: National Alcohol Screening Day

The Portland Alcohol Research Center (PARC), OHSU's Behavioral Health Clinic (BHC), and the OHSU School of Dentistry (SOD) co-sponsored OHSU's participation in National Alcohol Screening Day (NASD), April 5th, 2001.

The PARC Education Core (Mark Rutledge-Gorman, Administrator) coordinated the all-day event which offered the general public literature on alcohol and free evaluations of alcohol use.

Clinical staff from BHC conducted the evaluations of alcohol consumption for individuals themselves and for people who expressed concern for alcohol consumption patterns of friends or family members. When evaluations suggested problem alcohol use, clinicians offered referrals for further assessment and treatment in the community. Peter Barbur, Director of BHC, said, "This type of public event is critical to broadening community awareness of alcohol-related problems and the local resources available to individuals and their families and friends to receive help."

Theresa Madden, Department of Periodontology (OHSU SOD), noted that dentists are paying increased attention to the role of alcohol in people's oral health. She stated, "The combined use of alcohol and

tobacco increases 38-fold the risk for oral cancer. Furthermore, facial and oral trauma commonly result from alcohol-related accidents and violence. Dentists have such a good track record for prevention, and we can be quite effective at screening for and helping to prevent alcohol-related problems."



Theresa Madden

Pre-doctoral students Alison Atkins (PARC PI John Belknap, mentor), Amy Beadles-Bohling & Tarra Gupta (PARC PI Kristine Wiren, mentor), and Paul Meyer (PARC PI Tamara Phillips, mentor) were on hand to describe basic science alcohol research. The students answered questions about the brain's general responses to alcohol, and progress toward identifying genes that may confer greater risk of or protection against alcoholism. BHC clinicians and students also discussed their respective research interests and potential future collaborations between basic science researchers and clinicians aimed at understanding the genetics of alcoholism.

NASD is organized nationally by Screening for Mental Health (<http://www.nmisip.org/alcohol.htm>), a non-profit organization, which also coordinates screening days for mood, anxiety, and eating disorders.

Selected Publications

- Bachtell, R. K. and Ryabinin, A. E. (2001). **Interactive effects of nicotine and alcohol co-administration on expression of inducible transcription factors in mouse brain.** *Neuroscience* 103: 941-954.
- Browman, K. E., Rustay, N. R., Nikolaidis, N., Crawshaw, L., and Crabbe, J. C. (2000). **Sensitivity and tolerance to ethanol in mouse lines selected for ethanol-induced hypothermia.** *Pharmacology, Biochemistry and Behavior* 67: 821-829.
- Buck, K. J. and Finn, D. A. (2001). **Genetic factors in addiction: QTL mapping and candidate gene studies implicate GABAergic genes in alcohol and barbiturate withdrawal in mice.** *Addiction* 96: 139-149.
- Crabbe, J. C. (2001). **Use of genetic analyses to refine phenotypes related to alcohol tolerance and dependence.** *Alcoholism: Clinical and Experimental Research* 25: 288-292.
- Cunningham, C. L., Fidler, T. L., and Hill, K. G. (2000). **Animal models of alcohol's motivational effect.** *Alcohol Research and Health* 24: 85-92.
- Cunningham, C. L., Howard, M. A., Gill, S. J., Rubinstein, M., Low, M. J., and Grandy, D. K. (2000). **Ethanol-conditioned place preference is reduced in dopamine D2 receptor-deficient mice.** *Pharmacology, Biochemistry and Behavior* 67: 693-699.
- Cunningham, C. L. and Henderson, C. M. (2000). **Ethanol-induced conditioned place aversion in mice.** *Behavioural Pharmacology* 11: 591-602.
- Lessov, C. N., Risinger, F. O., and Phillips, T. J. (2001). **Attenuation of ethanol-induced conditioned taste aversion in mice sensitized to the locomotor stimulant effects of ethanol.** *Behavioral Neuroscience* 115: 146-153.
- Morikawa, H., Manzoni, O. J., Crabbe, J. C., and Williams, J. T. (2000). **Regulation of central synaptic transmission by 5-HT(1B) auto- and heteroreceptors.** *Molecular Pharmacology* 58: 1271-1278.
- Plomin, R. and Crabbe, J. (2000). **DNA.** *Psychological Bulletin* 126: 806-828.
- Rausch, R. N., Crawshaw, L. I., and Wallace, H. L. (2000). **Effects of hypoxia, anoxia, and endogenous ethanol on thermoregulation in goldfish, *Carassius auratus*** *American Journal of Physiology: Regulatory, Integrative, and Comparative Physiology* 278: R545-R555.
- Reilly, M. T., Crabbe, J. C., Rustay, N. R., and Finn, D. A. (2000). **Acute neuroactive steroid withdrawal in Withdrawal Seizure-Prone and Withdrawal Seizure-Resistant mice.** *Pharmacology, Biochemistry and Behavior* 67: 709-717.
- Risinger, F. O. and Cunningham, C. L. (2000). **DBA/2J mice develop stronger lithium chloride-induced conditioned taste and place aversions than C57BL/6J mice.** *Pharmacology, Biochemistry and Behavior* 67: 17-24.
- Risinger, F. O., Freeman, P. A., Rubinstein, M., Low, M. J., and Grandy, D. K. (2000). **Lack of operant ethanol self-administration in dopamine D2 receptor knockout mice.** *Psychopharmacology* 152: 343-350.
- Risinger, F. O., Freeman, P. A., Greengard, P., and Fienberg, A. A. (2001). **Motivational effects of ethanol in DARPP-32 knock-out mice.** *Journal of Neuroscience* 21: 340-348.
- Ryabinin, A. E. (2000). **ITF mapping after drugs of abuse: Pharmacological versus perceptual effects.** *Acta Neurobiologiae Experimentalis* 60: 547-555.
- Ryabinin, A. E., Bachtell, R. K., Freeman, P., and Risinger, F. O. (2001). **ITF expression in mouse brain during acquisition of alcohol self-administration.** *Brain Research* 890: 192-195.
- Schafer, G.L., Crabbe, J.C., Wiren, K.M. (2001). **Ethanol-regulated gene expression of neuroendocrine-specific protein in mice: brain region and genotype specificity.** *Brain Research* 897: 139-149.

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

A cumulative bibliography of all PARC publications is available at the PARC Web Site:
www.ohsu.edu/som-BehNeuro/PARC/Center.html

Awards

PARC Scientific Director, Chris Cunningham, has received the inaugural Oregon Health & Science University School of Medicine Alumni Scientist Award. The award recognizes continued excellence in research by a graduate student of OHSU, School of Medicine, or its predecessor. Dr. Cunningham is a graduate of the University of Oregon Medical School, Class of 1976. He delivered an address on, "The Origins of Graduate Degree Training in the Oregon Medical School".



Chris Cunningham

Chris Cunningham also shared with PARC PI Fred Risinger the 2001 OHSU Outreach Award for mentoring future scientists. The award recognized their leadership as co-directors for the Summer Research Apprenticeship Program at OHSU which provides research opportunities for minority students. Amy Beadles-Bohling (PARC PI Kristine Wiren mentor) also was nominated for an Outreach Award.

Stephen Boehm II was awarded a two-year pre-doctoral NRSA (National Research Service Award) from NIAAA. The title of the fellowship is "GABA-B modulation of ethanol-induced locomotion." Mr. Boehm's mentor is PARC PI Tamara Phillips.

Ryan Bachtell, a pre-doctoral student in the lab of PARC PI Andrey Ryabinin, also received an NRSA from NIAAA for a project entitled, "Characterizing the Edinger-Westphal Response to Alcohol."

Kari J. Buck (Director, PARC Molecular Genetics Support Core) has had an R29 awarded RO1 status, "Ethanol Withdrawal QTLs & Candidate Genes," 8/1/01-7/31/02, direct costs \$82,000 current year.

Jeri Janowsky, (Depts of Neurology and Behavioral Neuroscience) and John Crabbe, received a \$4,000,000 award from the US Navy, "Neuroimaging and Substance Abuse," 3/19/01-1/1/03, to establish a 3T MRI system for spectroscopy, morphological, & functional neuroimaging to study drug abuse risk.

Abraham Palmer, a post-doc in the lab of Tamara Phillips, received an NRSA from NIAAA for a project entitled, "Ethanol and allopregnanolone: Common genetic influences?" and a Tartar Research Fellowship Award for "Disruption of circadian rhythm, a modulator of ethanol preference and consumption?"

Tartar Trust Fellowships also were awarded to Ryan Bachtell for "Regulation of alcohol sensitivity by alpha (2)-adrenoceptor antagonists in the Edinger-Westphal nucleus," Andrey Ryabinin mentor; Amy Beadles-Bohling for "Analysis of the kappa-opioid system in ethanol withdrawal," Kristine Wiren mentor; Janel Boyce for "Chronic ethanol reinforcement in dopamine D3 receptor knockout mice," Fred Risinger mentor; Tarra Gupta for "Involvement of mineralocorticoid receptor in withdrawal severity after repeated ethanol withdrawal," Kristine Wiren mentor; Paul Meyer for "Accumbal dopamine efflux in response to systemic or intra-tegmental ethanol in FAST and SLOW mice," Tamara Phillips mentor; and Nathan Rustay for "Genetic, neurochemical, and neuroanatomical characterization of rapid tolerance to alcohol," John Crabbe mentor.

NIAAA/PARC Research Seminars

Todd Thiele, PhD, Dept of Psychology, Univ. of Washington, "**Behavioral characterization of protein kinase A-mutant mice,**" October 2000

Suzanne Mitchell, PhD, Dept of Psychology, Univ. of New Hampshire, "**Factors influencing the preference for drug and nondrug rewards,**" January 2001

Jacob Raber, PhD, Gladstone Institute of Neurological Diseases, Univ. of California, San Francisco, "**Gender- and isoform-dependent effects of apoE on brain function,**" January 2001

Donald Katz, PhD, Dept of Neurobiology, Duke Univ., "**The dynamics of cortical responses to tastants,**" January 2001

Ronald See, PhD, Depts of

Physiology and Neuroscience, Medical Univ. of South Carolina, "**Neural substrates of appetitive conditioning in an animal model of relapse to cocaine-seeking behavior,**" January 2001

Stephan Anagnostaras, PhD, Dept of Neurobiology, Univ. of California, Los Angeles, "**Neuroanatomic and genetic substrates of memory,**" January 2001

Scott Wersinger, PhD, Section on Neural Gene Expression, NIMH, Bethesda, "**The role of the vasopressin V1b receptor in the regulation of behavior and the hypothalamic-pituitary-adrenal axis,**" January 2001

William Timberlake, PhD, Dept of Psychology, Indiana Univ., "**Niche-related learning in laboratory**

mazes," February 2001
Kara Gabriel, PhD, Alcohol and Drug Abuse Research Center, Harvard Medical School, "**Effects of postnatal handling on animals prenatally exposed to ethanol,**" February 2001

S. Paul Berger, MD, Depts of Psychiatry and Neuroscience, Univ. of Cincinnati and Cincinnati VA Medical Center, "**Translational research from cocaine sensitization to clinical trials,**" February 2001

Peter Rapp, PhD, Kastor Neurobiology of Aging Laboratories, Mount Sinai School of Medicine, "**Toward a neurobiology of cognitive aging in the nonhuman primate,**" March 2001

Herman Samson, PhD, Dept of Physiology &

Pharmacology, Wake Forest Univ. School of Medicine, "**Behavioral regulation of alcohol consumption,**" March 2001

Howard Becker, PhD, Dept of Psychiatry, Center for Drug and Alcohol Programs, Medical Univ. of South Carolina, "**Repeated ethanol withdrawals: Neuroadaptive consequences and treatment implications,**" April 2001

Michael Miles, MD, PhD, Ernest Gallo Clinic and Research Center, "**A functional genomics approach to the neurobiology of drug abuse,**" April 2001

Nora Volkow, MD, Brookhaven National Laboratory, "**Inside the addicted brain,**" April 2001

Regional Resources

The Crisis Triage Center
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

Education & Outreach: brain awareness

In Portland, national Brain Awareness Week events for all ages were held at the Oregon Museum of Science and Industry (OMSI), March 10-15, 2001. Oregon Health & Science University (OHSU) and the Oregon chapter of the Society for Neuroscience (SFN) joined OMSI as local sponsors.



Amy Beadles-Bohling (left), OHSU President Peter Kohler, and visiting scientist from Spain, Rosario Pasaro, confer before the Brain Bee competition at Brain Awareness Week

Photo: Bobby Heagerty, OHSU

Robert Hitzemann, a member of the PARC Scientific Advisory Board and Chair of OHSU's Dept of Behavioral Neuroscience, was one of several featured neuroscientists from around the country. Dr. Hitzemann discussed how brain cells change and adapt to alcohol and other substances.

The PARC's Education Core (Mark Rutledge-Gorman, Administrator) provided organizational support and put together

an alcohol display for children and adults. The display focused on the consequences for the brain of problem alcohol use, and provided interactive games simulating the psychomotor impact of alcohol. Amy Beadles-Bohling, a pre-doctoral student mentored by Kristine

Wiren (PARC Investigator), Stacy Matthews, a research assistant in the lab of Deborah Finn (PARC Investigator) and Charles Meshul (PARC Investigator) hosted the PARC display.

Ms. Beadles-Bohling was instrumental in organizing the Brain Fair, which attracted several thousand children and adults. She helped create many of the interactive neuroscience displays, which made the fair particularly engaging for children. Ms. Beadles-Bohling is also the graduate student representative on OHSU's committee on Science Outreach and Resources (SOAR). SOAR provides education to the community about biomedical research at OHSU.

Cheryl Reed (Research Associate in the Hitzemann lab) was in charge of the Brain Bee competition which tested students' knowledge of the brain. The winner continued on to the national Brain Bee, sponsored by SFN.

Ryan Bachtell (pre-doctoral student mentored by PARC Investigator Andrey Ryabinin) hosted an interactive display about neurons, and Paul Meyer (pre-doctoral student mentored by PARC Investigator Tamara Phillips) introduced visitors to brain anatomy. Tarra Gupta and Tara Macey, pre-doctoral students of Kristine Wiren (PARC Investigator) and Kim Neve (PARC Investigator), respectively, created an interactive display on alcohol and substance abuse and represented the Department of Behavioral Neuroscience.

The Portland Alcohol Research Center is supported by a grant from the National Institute on Alcohol Abuse and Alcoholism, P50 AA10760.

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.

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