

## Alcohol Consumption and Initial Sensitivity

**Kathleen A. Grant, Ph.D.**, a Professor in OHSU's Department of Behavioral Neuroscience, and a Senior Scientist in the Division of Neuroscience at the Oregon National Primate Research Center (ONPRC), joins the Alcohol Center as a full research component principal investigator in 2010. Dr. Grant's project, "Sensitivity and Ethanol Self-administration in Rhesus Monkey," developed from her work on a pilot project funded by the Center in 2009.

Dr. Grant earned her Ph.D. in physiological psychology from the University of Washington in 1984 under the mentorship of Hank Sampson. Her research focused on animal models of alcohol self-administration and schedule-induced polydipsia. During a 3-year postdoctoral fellowship at the University of Chicago, Dr. Grant began her studies of alcohol self-administration in macaque monkeys under the guidance of Charles Schuster and Chris-Ellyn Johanson. Her post-doctoral projects documented individual differences, including sex and drug history, as risks for heavy alcohol consumption. It was also during these years that Dr. Grant investigated behaviors observed under interval schedules that ultimately formed the basis of the drinking induction procedure currently used in her self-administration studies.

Dr. Grant took an appointment as a Staff Fellow at the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in 1987, becoming a Senior Staff Fellow in 1990. At the NIAAA intramural program, she worked with Boris Tabakoff and Paula Hoffman in studies of the cellular and molecular pharmacology of alcohol. She then joined the faculty at Wake Forest University School of Medicine in 1991, where she advanced from assistant professor to professor in the Department of Physiology and Pharmacology. Before coming to OHSU, Dr. Grant was Director of the Wake Alcohol Research Center. Since 2002, she has been Director of the Integrative Neuroscience on Alcoholism consortium project (INIA-Stress), an NIAAA-sponsored effort that links multiple research sites and investigators in a common set of neuroscience efforts. Dr. Grant has held her current positions at OHSU and ONPRC since 2005.

Dr. Grant was elected by her peers as President of the Research Society on Alcoholism (RSA) in 2005. She has chaired the NIAAA Board of Scientific Counselors which helps guide NIAAA's scientific agenda, and in 2008 was honored by NIAAA with the Mark Keller Award.

In her PARC pilot project, Dr. Grant has been assessing the self-administration of alcohol in young adult rhesus monkeys that were character-

ized by Dr. Judy Cameron (PARC project 2005-09) for sensitivity to alcohol intoxication early in life (an age equivalent to human pre-adolescents). The results show that a subject's eventual daily alcohol consumption is directly proportional to the subject's initial sensitivity. This very strong risk factor doesn't seem to affect initial stages of drinking, but becomes clear after drinking has been established and escalated after six months. Final alcohol intake levels in these monkeys average over 12 drink equivalents/day with very

high blood alcohol levels. This level of alcohol consumption captures a heavy drinking phenotype that has been documented among human alcoholics.

The Grant lab uses a self-administration paradigm to investigate the risk for excessive alcohol consumption, including the influence of genetic composition, sex, age, and stress. This approach exposes all animals to the same procedure to induce alcohol self-administration, but then allows them to choose whether to drink heavily, lightly, or not at all. In this approach, individual subjects have demonstrated a wide range of alcohol drinking analogous to human alcoholic consumption. Further, these studies investigate the consequences of heavy drinking by looking at changes in gene expression for numerous proteins, through brain imaging studies, and by studies of liver damage and hormonal changes.

A second paradigm used by the lab is drug discrimination. In this method, Dr Grant and her colleagues characterize the in vivo pharmacological basis for ethanol's subjective effects and identify the neurotransmitter systems that mediate the subjective feelings of intoxication in mice, rats and monkeys. Once identified, the lab determines whether the intoxicating effects of ethanol are enhanced or antagonized by pharmacological pretreatment, genetic background, or organismal state such as endocrine status. Dr. Grant's research team has identified which major excitatory and inhibitory neurotransmitter receptor systems that mediate intoxication, and her studies have shown that endogenous steroids can influence the behavioral effects of alcohol.



**Kathleen Grant**

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## Center Director's Notes

2009 has been a busy year for PARC investigators as we have been preparing the application for renewal of the PARC Center Grant. I spent the year on sabbatical, so my most sincere thanks are extended to Bob Hitzemann (Acting Director) and Tamara Phillips (Acting Scientific Director) for overseeing this rather complex process. In addition, our Scientific Advisory Board (Adron Harris, Bob Messing, Harriet de Wit, Toni Shippenberg, and Rob Williams) have been wonderful about offering advice on short notice. And Mark Rutledge-Gorman continues to pull it all together for us all.

A notable development has been the evolution of Kathy Grant's pilot project into a full Research Component of the center. We are all quite excited about the data coming out of her project (see page 1 Cover Story). Another exciting event was the successful application to the Murdoch Trust for purchasing an Illumina Gene Analyzer Ix. This will allow us to do Next-Generation transcriptome sequencing (mRNA-seq) and will be a particular benefit to the research in Kari Buck's and Bob Hitzemann's components, as well as with Kathy Grant's monkey work. Bob Hitzemann wrote the proposal and spearheaded the effort to obtain this equipment for OHSU. We are looking forward to 2010.



**John Crabbe,**  
PARC Director

## Selected Center Publications

Crabbe JC, Metten P, Rhodes JS, Yu CH, Brown LL, Phillips TJ, Finn DA. (2009) **A line of mice selected for high blood ethanol concentrations shows drinking in the dark to intoxication.** *Biological Psychiatry* 65:662-70.

Denmark DL, Milner LC, Buck KJ. (2009) **Interval-specific congenic animals for high-resolution QTL mapping.** *Alcohol Research & Health* 31:266-269.

Holstein SE, Dobbs L, Phillips TJ. (2009) **Attenuation of the stimulant response to ethanol is associated with enhanced ataxia for a GABA, but not a GABA<sub>A</sub> receptor agonist.** *Alcohol Clin Exp Res* 33:108-20.

Hitzemann R, Edmunds S, Wu W, Malmanger B, Walter N, Belknap J, Darakjian P, McWeeney S. (2009) **Detection of reciprocal quantitative trait loci for acute ethanol withdrawal and ethanol consumption in heterogeneous stock mice.** *Psychopharmacology (Berl)* 203:713-22.

Walter NA, Bottomly D, Laderas T, Mooney MA, Darakjian P, Searles RP, Harrington CA, McWeeney SK, Hitzemann R, Buck KJ. (2009) **High throughput sequencing in mice: a platform comparison identifies a preponderance of cryptic SNPs.** *BMC Genomics* 10:379.

Chen G, Reilly MT, Kozell LB, Hitzemann R, Buck KJ. (2009) **Differential activation of limbic circuitry associated with chronic ethanol withdrawal in DBA/2J and C57BL/6J mice.** *Alcohol* 43:411-420.

Wilhelm CJ, Mitchell SH. (2009) **Strain differences in delay discounting using inbred rats.** *Genes, Brain and Behavior* 8:426-34.

Wilhelm CJ, Mitchell SH. (2009) **Rats bred for high alcohol drinking are more sensitive to delayed and probabilistic outcomes.** *Genes, Brain and Behavior* 7:705-13.

Sharpe AL, Phillips TJ. (2009) **Central urocortin 3 administration decreases limited-access ethanol intake in nondependent mice.** *Behavioral Pharmacology* 20:346-51.

Belknap JK, Metten P, Beckley EH, Crabbe JC. (2008) **Multivariate analyses reveal common and drug-specific genetic influences on responses to four drugs of abuse.** *Trends in Pharmacological Sciences* 29:537-43.

Cunningham CL, Gremel CM, Groblewski PA. (2008) **Genetic influences on conditioned taste aversion.** In S Reilly & TR Schachtman (Eds.), *Conditioned taste aversion: Behavioral and neural processes* (pp. 387-421). New York: Oxford University Press.

Bohlen M, Cameron A, Metten P, Crabbe JC, Wahlsten D. (2009) **Calibration of rotational acceleration for the rotarod test of rodent motor coordination.** *J Neuroscience Methods* 178:10-4.

Meyer PJ, Meshul CK, Phillips TJ. (2009) **Ethanol- and cocaine-induced locomotion are genetically related to increases in accumbal dopamine.** *Genes, Brain and Behavior*. Feb 11. [Epub ahead of print]

Beckstead MJ, Phillips TJ. (2009) **Mice selectively bred for high- or low-alcohol-induced locomotion exhibit differences in dopamine neuron function.** *Journal of Pharmacology and Experimental Therapeutics* 329:342-9.

Scibelli AC, Phillips TJ. (2009) **Combined scopolamine and ethanol treatment results in a locomotor stimulant response suggestive of synergism that is not blocked by dopamine receptor antagonists.** *Alcoholism: Clinical and Experimental Research* 33:435-47.

## Center Publications, cont.

Carney PA, Bunce AE, Perrin N, Howarth LC, Beemsterboer P, Griest S, **Cameron W**. (2009) **Educating the public about research funded by the National Institutes of Health using a partnership between an academic medical center and community-based science museum.** *Journal of Community Health* 34:246–254.

**Crabbe JC**, Bell RI, Ehlers CL. (2010) **Human and laboratory rodent low responses to alcohol: Is better consilience possible?** *Addiction Biology*, in press.

Bunce AE, Griest S, Beemsterboer P, Perrin N, Howarth LC, **Cameron W**, Carney PA. (2009) **Educating youth about research funded by the National Institutes of Health using a partnership between an academic medical center and community-based science museum.** *Journal of Community Health* 34:262–270.

Kozell LB, Walter NAR, Milner LC, Wickman K, **Buck KJ**. (2009) **Mapping a Barbiturate Withdrawal Locus to**

**a 0.44 Mb Interval and Analysis of a Novel Null Mutant Identify a Role for Kcnj9 (GIRK3) in Withdrawal from Pentobarbital, Zolpidem, and Ethanol.** *Journal of Neuroscience* 29:11662–11673.

Gremel CM, **Cunningham CL**. (2009) **Involvement of amygdala dopamine- and nucleus accumbens NMDA-receptors in ethanol-seeking behavior in mice.** *Neuropsychopharmacology* 34:1443-1453.

Groblewski PA, Lattal KM, **Cunningham CL**. (2009) **Effects of D-Cycloserine on the extinction and reconditioning of ethanol-seeking behavior in mice.** *Alcoholism: Clinical & Experimental Research* 33:772-782.

Ehlers CL, Walter NAR, Dick D, **Buck KJ**, **Crabbe JC**. (2010) **A comparison of selected quantitative trait loci associated with alcohol use phenotypes in humans and mouse models.** *Addiction Biology*, in press.

## 2009 PARC Pilot Project Awards

### PI: Bonnie Nagel, The Impact of Family History of Alcohol Use Disorders on Adolescent Reward Based Decision Making

Studies have shown that youth and young adults with family history of Alcohol Use Disorder (AUD) who are not yet using substances have impaired executive functioning, structural brain abnormalities, and abnormal brain functioning, suggesting that premorbid neural abnormalities may underlie the heritable aspects of AUD. The proposed study will use functional MRI methods to examine the influence of family history of alcohol use disorders on the neural substrates of adolescent reward-based decision making. Future studies aimed at following this cohort will also us to characterize developmental timing effects of alcohol initiation throughout the adolescent years. This study may help to further understanding of the impact of genetic risk factors and alcohol use on adolescent neurodevelopment and is an integral first step in developing better prevention and treatment strategies.

### PI: Kathy Grant, Initial Sensitivity to the Intoxicating Effects of Ethanol to Predict Alcohol Self-administration in Adulthood

Initial sensitivity and its relation to the development of alcohol use disorders in human subject studies has most often been measured with subjective responses, motor incoordination, or hormonal response. While a relationship between initial sensitivity to ethanol and the risk for future heavy drinking is widely accepted, this interaction remains relatively unexplored in the nonhuman primate. Data obtained in the first year of the pilot suggest that the younger the monkeys are when they started self-administering ethanol, the greater the subsequent average daily drinking. In the next year we plan to add an analysis of the results of anxiety tests conducted just prior to the onset of drinking and correlate these measures with HPA axis response.

### PI: Charles Allen and Deb Finn, Ethanol Interactions with the Circadian Timing System

This proposed project aims to examine how ethanol's actions on the circadian system is mediated at the cellular level, which may lead to development of new treatments of circadian based symptoms of diseases resulting from ethanol consumption. Suprachiasmatic nucleus (SCN) neurons of mammals contain a molecular circadian clock that provides animals a mechanism to synchronize physiological processes with environmental conditions. We hypothesize that the central circadian oscillator located in the SCN regulates the timing of ethanol consumption, and we propose to determine whether the circadian clock drives the increased ethanol drinking observed early in the night, when animals have limited access to ethanol.

The Portland Alcohol Research Center is supported by a grant from the National Institute on Alcohol Abuse and Alcoholism, P60 AA010760.

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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## National Resources

National Institute on Alcohol Abuse and Alcoholism  
Information, research programs, databases, links  
[www.niaaa.nih.gov](http://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](http://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](http://www.oadap.hr.state.or.us)

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

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## Awards to Center Scientists and Trainees

**Bonnie Nagel, NIH grant award, R01 AA017664**, "Timing Effects of Heavy Alcohol Initiation on Adolescent Neurodevelopment," National Institute on Alcohol Abuse and Alcoholism, 2009-2014

**Kari Buck, ARRA NIH grant award, R01 AA11114-10S1**, "The Role of Mpdz in Ethanol Withdrawal and Genetically Correlated Behaviors," National Institute on Alcohol Abuse and Alcoholism, 2009-2010

**Robert Hitzemann, Murdoch Trust award**, for acquisition of Illumina Gene Analyzer Ix to allow Next-Generation transcriptome sequencing (mRNA-seq), 2009

**Kari Buck, VA Merit Review grant award, 1I01BX000222**, "Genetic Vulnerability to Alcohol Withdrawal and Genetically Correlated Behaviors" Department of Veterans Affairs, 2009-2013

**John Crabbe, ARRA NIH grant award, U01AA013519-09S1**, "Selective Breeding for Drinking in the Circadian Dark," National Institute on Alcohol Abuse and Alcoholism, 2009-2011

**Kathleen Grant, NIH grant award, P60 AA010760 new research component**, "Sensitivity and Ethanol Self-administration in Rhesus Monkey," National Institute on Alcohol Abuse and Alcoholism, 2010

## PARC Education and Outreach

**Equity Summer Research, 2009.** For the fifth consecutive year, PARC partnered with the School of Medicine Dean's Office to support 3 students selected for the Equity Summer Research Program, which targets disadvantaged undergraduate students interested in biomedical research. During the recent nationwide economic downturn, the PARC's support for this program was instrumental in its survival. The long-term goal of this full time 8-week summer program is to increase the diversity of the graduate student body.

**Teacher Institute for the Experience of Science.** In 2009, PARC investigators presented to 12 middle school teachers experimental design and the social context of working with animals as a research subject. Teacher Institute for the Experience of Science or TIES (<http://ties.ohsu.edu/>).

**Of Brains and Safety: Neuroscience for Kindergarten – 3rd Grade.** This PARC created, scientist-led curriculum provides flexible, age-appropriate activities that link neuroscience and safety. In 2009 the PARC trained 8 graduate students and lab technicians, and conducted programs with 80 elementary age children.

**Alcohol Screening, Spring 2009.** PARC locally in Portland sponsored activities, information and screening at a multi-cultural Public Health fair and at one middle school science night. Approximately 200 people visited the PARC exhibits.

**Brain Awareness Season, March 2009.** In addition to joining the Brain Fair held on one Saturday at the Oregon Museum of Science and Industry, the PARC hosted the "Lost Weekend" during OHSU month at the museum in which addiction researchers staffed 4 exhibits for the weekend to explain their research and enroll subjects in control groups for drug studies. Staff interacted with about 300 people at each event.

**Middle School Biology of Alcohol.** PARC scientists and PARC-trained teachers presented on the biology of how the brain and body handle alcohol. In 2009, programs reached over 500 middle school students.