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The Importance of Animals in Advancing Alcohol Use Disorder Research

Christa M. Helms^{1,12}, Richard L. Bell^{2,12}, Allyson J. Bennett³, Daryl L. Davies^{4,12}, Julia A. Chester^{5,12}, Therese A. Kosten^{6,12}, Robert F. Leeman^{7,12}, Sangeeta Panicker⁸, Donna M. Platt^{9,12}, Jeff L. Weiner^{10,12}, and Scott Edwards^{11,12}

¹Division of Neuroscience, Oregon National Primate Research Center, Oregon Health & Science University

²Department of Psychiatry, Indiana University

³Department of Psychology, University of Wisconsin-Madison

⁴Titus Family Department of Clinical Pharmacy and Pharmaceutical Economics & Policy, School of Pharmacy, University of Southern California

⁵Department of Psychological Sciences, Purdue University

⁶Department of Psychology, University of Houston

⁷Department of Psychiatry, Yale School of Medicine

⁸Science Directorate, American Psychological Association

⁹Department of Psychiatry and Human Behavior, University of Mississippi Medical Center

¹⁰Department of Physiology and Pharmacology, Wake Forest School of Medicine

¹¹Department of Physiology, Louisiana State University Health Sciences Center at New Orleans

¹²Research Society on Alcoholism Animal Research and Ethics Committee

Alcohol use disorder (AUD) occurs in about 18 million adults in the United States, while excessive drinking contributes to approximately 6% of all deaths worldwide (World Health Organization 2014). Alcohol use directly contributes to multiple organ pathologies (e.g., cardiovascular disease; Djoussé et al. 2009; Molina et al. 2014) in a dose-dependent fashion and is among the leading causes of premature death and disability in the United States (Bauer et al. 2014). AUD is fundamentally a behavioral disease, often referred to as a chronic relapsing disorder (Edwards and Gross 1976). As such, it can only be modeled by reproducing observable characteristics of the disease, such as excessive or impaired control over drinking, withdrawal symptoms, and relapse-like behavior (Edwards and Koob 2012; Leeman et al. 2014; Grant et al. 2014). Most physiological diseases originate from abnormal cellular processes that are largely independent of volitional behavior. In contrast, AUD develops through the gradual shaping of alcohol drinking over years as a cause and

consequence of changes in the brain, resulting in a shift in the distribution of an individual's behavior away from more natural incentives like career and family. Indeed, AUD diagnoses are almost exclusively based on behavior and patterns of drinking over time (APA 2013). There remains an urgent need to develop a comprehensive understanding of the mechanisms driving AUD, as well as to develop a variety of clinical tools to combat this disease.

Like other neurobehavioral disorders, AUD results from a complex interplay of genetics and environment (Bell et al. 2012). How these variables alter patterns and frequency of drinking related to AUD manifestation is a central research emphasis at both clinical and preclinical levels. Today, self-reporting of alcohol consumption is used as a proxy of drinking patterns and has led to many fundamental insights, including the identification of sex differences and comorbidities (Goldstein et al. 2012), albeit with limitations. Self-report can categorize individuals in terms of alcohol consumption (Babor and Mendelson 1979) but there is no substitute for daily, long-term measures of drinking behavior and blood-alcohol concentrations as accomplished in animal studies (Leeman et al. 2010). Appropriate animal models sidestep the limitations of human studies such as self-report bias and can identify physiological factors that determine patterns of alcohol consumption while controlling for comorbidities and life history. The motivation for alcohol consumption is complex in both humans and animals, with specific contributions from metabolic, social and stress-related factors. A continuing work-in-progress within our field is to test the validity of various animal models and to select those most related to harmful alcohol use (e.g., animals consistently drinking at or above blood-alcohol concentrations exceeding the legal limit for intoxication, 80 mg/dl). These studies are essential for increasing our basic knowledge of mechanisms of alcohol reinforcement, and in turn, these discoveries will increase the likelihood of developing new and effective treatments for controlling excessive alcohol consumption.

In recent years, members of the non-profit group Physicians Committee for Responsible Medicine (PCRM) have regularly petitioned the NIAAA Advisory Council to exclude alcohol research in animals from their portfolio, and to instead focus on education and treatment in humans. Indeed, prevention and rehabilitation are important steps and strategies that are well funded by NIAAA and other groups. However, sustained commitment to basic research is necessary, and animals are required where there are no viable alternatives. We can glean important insight into the neural basis of self-reported alcohol consumption in humans using non-invasive neuroimaging techniques (Marinkovic et al. 2009; Niciu and Mason 2014), but both the behavioral measures and the resolution afforded by these methods is limited. By integrating animal models of excessive alcohol consumption with emerging, cutting-edge neurobiological methods (e.g., proteomics; Gorini et al., 2014) researchers are rapidly gaining new insight into the specific neural circuits and signaling pathways that control critical aspects of alcohol-drinking behavior. As just one recent example, using optogenetic studies in rats, a neurotransmitter-specific (i.e., glutamate) projection from the insular cortex to the nucleus accumbens core was shown to regulate aversion-resistant drinking, an animal model of persistent drinking despite adverse consequences (a behavior that is central to the diagnosis of AUD; Seif et al. 2013). These results exemplify the complexity of neurochemical signaling within the brain, which, in combination with humoral/hormonal cross-talk between non-neuronal and neuronal

elements (Crews, 2012), represent irreducible systems unlikely to be recapitulated *in vitro* or even using the most sophisticated computer models. Animal models also are important for steering alcoholism therapies into the era of personalized medicine by defining gene×environment interactions (Hendershot 2014) far more complicated than what can be reliably modeled *in vitro* or *in silico*.

In addition to ushering in new targets for medical intervention, animal models are vital for the refinement of incomplete treatment conceptualizations that currently exist at the clinical level. A limitation of pharmacotherapies is that they target any cell in any part of the brain that contains the receptor at which the drug exhibits efficacy, leading to off-target effects. For example, naltrexone and naloxone, both non-selective opioid receptor antagonists, have repeatedly been shown to decrease both alcohol drinking and consumption of other concurrently available fluids in animal studies. Naltrexone is FDA-approved for AUD and is reported to reduce the number of heavy drinking days (Jonas et al. 2014). However, it is not effective in all patients and has substantial compliance issues (Swift et al., 2011). Opioid receptor-based medications with more selective mechanisms of action based on an understanding of the neurobiological basis of excessive drinking are still needed (Butelman et al., 2012). Preclinical studies are continuing to disentangle distinct opioid signaling mechanisms in dependence-related behavior (e.g., Walker and Koob, 2008), with several promising new medications currently undergoing clinical trials that target opioid (e.g., nalmefene) and non-opioid mechanisms (Litten et al. 2012; Davies et al. 2013). Importantly, preclinical animal models of dependent vs. non-dependent drinking have specified a role for many new drug candidates as targeting pathological excessive drinking vs. non-specific reward mechanisms (Vendruscolo and Roberts, 2014).

Progress in advancing the understanding of alcoholism with the aim of developing treatments using animal models must be, and is, carried out with a high degree of ethical oversight. In addition to the ongoing humane care and use of all research animals in our protection, Institutional Animal Care and Use Committees at institutions where studies are conducted require scientists to adhere to the principles of the 3Rs: reduction, replacement, and refinement (Russell and Burch, 1959). Within this ethical framework, investigators limit the number of animals to what is required for scientifically valid results, seek replacements for animal models (e.g., computer simulations), and constantly refine methods and techniques to minimize discomfort (e.g., environmental enrichment). Another obligation that stems from the use of animal models is the constant need to improve our experimental strategies to more closely match success rates at the preclinical and clinical levels (Egli, 2005). Rigorous and expert peer review before both grant award and publication make the science of alcohol dependence a community effort with feedback at various stages of a project. In a similar vein, because we study complex behavior over extended time periods, alcohol researchers are keenly aware of the importance of animal health in the generation of valid data, which contributes to best practices in animal welfare.

A long history of overwhelming evidence points to the benefits of animal research for both human and veterinary medicine (Royal Society 2004). What are needed now are patience and a renewed commitment to proven strategies that advance biology and medical technology. The most complicated diseases, such as those involving the brain, should require

more time and effort to investigate. Human and non-human studies have discovered sex differences, effects of social status, stress and early-life experiences that affect the incidence, severity and outcomes of excessive alcohol consumption. Research on the impact of alcohol on communities (Flynn and Wells 2013), control of land use (Ashe et al. 2003) and brief interventions by physicians (Gaume et al. 2014) can reduce excessive alcohol within a population, but among vulnerable individuals, AUD may still develop. Alcohol use is particularly complicated because regular non-heavy drinking is associated with decreased mortality while particular patterns place individuals at risk (Plunk et al., 2014). Alcohol use has long been a dominant aspect of our vibrant culture, yet the transition to AUD reduces the quality of life for individuals, families and communities. Consistent with an aim of NIAAA (www.niaaa.nih.gov/about-niaaa), it is our responsibility to use all available skills to understand why and how some individuals become addicted, and how to reverse or decrease the cellular pathology mediating the behavior. This is a time of rapid advances in technology, so we expect new insights into the biological mechanisms of AUD if we continue to use animals in basic research. The combined efforts of scientists, clinicians, and bioethicists will ensure that the translational process of discovery and treatment will continue to include humane animal-based investigation.

Finally, we urge all individuals who wish to continue the use of animals in alcohol research to become more actively engaged in the dialogue. Below, we provide links to organizations that champion the utilization of animals to promote future medical breakthroughs:

Speaking of Research

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