NIAAA Director’s Report
on Institute Activities to the 141st Meeting
of the National Advisory Council on
Alcohol Abuse and Alcoholism

February 12, 2016
Rockville, MD

George F. Koob, Ph.D.
Director
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health
NIAAA FY 2015 Budget

• Fiscal Year (FY) 2015 closed out on September 30, 2015.

• FY 2015 appropriation: $447.2 M.

• NIAAA awards and funding:
  – 668 research project grants, including 156 competing awards.
  – Success rate: 18 percent.
  – 18 research centers: $28.0 million.
  – 135 other research grants: $37.2 million.
    • Includes career awards, 1 cooperative clinical agreement, and resource and conference grant awards.
  – 277 full-time training positions: $12.7 million.
  – R&D contract portfolio: $36.6 million.
  – NIAAA support for intramural research: $49.5 million.
Comparison of FY 2015 and FY 2016 Budgets

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<tr>
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<th>FY 2015</th>
<th>FY 2016</th>
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<tr>
<td><strong>NIH</strong></td>
<td>$30.3 billion</td>
<td>$32.3 billion</td>
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<td>$2 B over FY 15</td>
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<tr>
<td><strong>NIAAA</strong></td>
<td>$447.2 million</td>
<td>$467.7 million</td>
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<td>$20.5 M (4.9%) over FY 15</td>
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<tr>
<td><strong>NIAAA Research Project Grants</strong></td>
<td>668</td>
<td>684 (estimated)</td>
</tr>
<tr>
<td><strong>NIAAA Competing Awards</strong></td>
<td>156</td>
<td>173 (estimated)</td>
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FY 2017 Budget

• Preliminary work has begun on the FY 2017 budget.

• President’s budget request will be presented to Congress in February 2016.
Staff Transitions

New Positions

• Mohammed Akbar, Med. ScD, joined the Division of Metabolism and Health Effects as a Program Officer in August, 2015. Trained as a Physiologist and Cell Biologist, he focuses on the pharmacological and toxicological aspects of alcoholic liver disease and alcohol-induced tissue injury.

• Janos Paloczi, PhD, joined the Laboratory of Cardiovascular Physiology and Tissue Injury as Visiting Research Scientist on August 17, 2015. He received his Ph.D. in Theoretical Medical Sciences at the University of Szeged in 2015.

• Balazs Nemeth, MD, joined the Laboratory of Cardiovascular Physiology and Tissue Injury as an NIH Graduate Student in January 2016. He is a PhD student at Semmelweis University Heart and Vascular Center.

• Grace Tato joined the NIAAA Administrative Services Branch. She comes to NIAAA from NCI, where she served as Administrative Officer for the Division of Extramural Activities.
Staff Transitions

New Positions

• **Christie Cunningham-Charles** joined the NIAAA Administrative Services Branch. She comes to NIAAA from NCI, where she served as Administrative Officer in the Center for Cancer Research.

Staff Retirements

• **Ken Warren, PhD**, has retired after 41 years of federal service, 39 of them at NIAAA. Dr. Warren served as NIAAA Deputy Director for 7 years, and as NIAAA Acting Director for more than 5 years. He has returned to NIAAA as a non-federal employee.

• **Ellen Witt, PhD**, has retired. Dr. Witt joined NIAAA in 1989 and served as Deputy Director of the Division of Neuroscience and Behavior since 2008.

• **Debbie Hendry** has retired. Ms. Hendry joined the NIAAA Grants Management Branch as a Grants Management Specialist in 1998. She has returned to NIAAA as a non-federal employee.
Honors & Awards

- **Dr. Beata Buzas** received the NIH Office of the Director Honor Award as part of the NIH Vertebrate Animal Section Update Workgroup.

- **Dr. Resat Cinar** was awarded an American Thoracic Association grant to study the therapeutic potential of a novel antifibrotic medication to treat Hermansky-Pudlak syndrome with pulmonary fibrosis.

- **Dr. Mehdi Farokhnia**:
  - Received American Society of Clinical Psychopharmacology New Investigator Award.
  - Received NIDA-International Society of Addiction Medicine Fellowship for Young Investigators.
  - Named winner, abstract with the highest rating for international scientific merit.

- **Dr. Bob Freeman** received the NIH Director’s Award as a member of the NIH Sexual and Gender Minority Research Coordinating Committee.
• **Drs. Peggy Murray, Kenneth Warren, Antonio Noronha, and John Matochik** received the NIH Director’s Award in recognition of their work on the NIH team that developed, implemented, and awarded the grants for the ABCD Study.

• **Dr. Pal Pacher:**
  – Received title of **Doctor Honoris Causa**, from **Semmelweis University** for extraordinary achievements in natural and technological sciences.
  
  – Included among the 128 highly cited researchers in “Highly Cited Researchers 2015” by Thomson Reuters in the field of Pharmacology and Toxicology.
College Alcohol Intervention Matrix Briefing

- **CollegeAIM** released in September 2015.

- Friends of NIAAA, in cooperation with the Congressional Addiction, Treatment, and Recovery Caucus, hosted a congressional briefing: “**CollegeAIM**: Evidence-based strategies for targeting high-risk drinking on college campuses.”

- Drs. George Koob, Jonathan Gibraltar, and Mary Larimer were featured speakers.
New FOAs Issued by NIAAA

- Integrative Neuroscience Initiative on Alcoholism (INIA) Consortia (U01/U24)
- Multi-Site Randomized Controlled Clinical Trial Research Center on Alcohol's Health Effects (U10)
RSU1 REGULATES ETHANOL CONSUMPTION IN DROSOPHILA AND HUMANS

The authors used a well-established drosophila model to determine that the Ras suppressor 1 (Rsu1) gene is important for alcohol-related behaviors such as alcohol sensitivity and preference. Polymorphisms in Rsu1 identified in human adolescents are associated with alterations in brain activation during reward anticipation, and AUD subjects showed a genetic association with a potential rare variant in Rsu1. (Ojelade SA, et al. Proc Natl Acad Sci U S A. 2015 Jul 28;112(30):E4085-93)

<table>
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<th>IMAGEN</th>
<th>NFBC</th>
<th>SAGE (Caucasian)</th>
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<tr>
<td>Life-time frequency of drinking (N=1908)</td>
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<tr>
<td>Quantity of alcohol consumption (g/d) (N=4604)</td>
<td></td>
<td>*MC=0.018 P=0.0140</td>
<td>Not Significant</td>
</tr>
<tr>
<td>Alcohol dependence vs. control (N=2346)</td>
<td></td>
<td></td>
<td>*MC=0.020 P=0.020</td>
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<tr>
<td>Haplotype Analysis</td>
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<tr>
<td>Hap4 (P=0.0343)</td>
<td></td>
<td>Hap4 (P=0.0360)</td>
<td>Hap3 (P=2.71x10^{-3}) Omnibus (P=5.99x10^{-3})</td>
</tr>
</tbody>
</table>

*MC stands for generalized mean correlation as a measure of effect size.

Summary of genetic analyses of alcohol drinking in human datasets

Knockdown of Rsu1 or overexpression of Rac1^{ca} causes loss of acquired ethanol preference

[Graph showing MB-Gene Switch and preference index over days]
LEPTIN LEVELS ARE REDUCED BY INTRAVENOUS GHRELIN ADMINISTRATION AND CORRELATED WITH CUE-INDUCED ALCOHOL CRAVING

Increasing evidence supports the role of appetite-regulating pathways in addictions. This study provides evidence of ghrelin-leptin cross-talk in individuals with AUD and suggests that the relationship between ghrelin and leptin may play a role in alcohol craving. These results hold important clinical value because cue-induced craving may be associated with relapse and may predict alcohol-related outcomes. In addition, while studies have tended to focus on the role of individual appetite-regulating peptides in alcohol consumption, this study paves the way for future translational research on the role of interactions between these peptides in alcohol consumption. (Haass-Koffler CL et al. Transl Psychiatry. 2015;5:e646)

Changes in serum leptin levels after infusion of ghrelin vs. placebo

![Graph showing changes in serum leptin levels](image)
Acute physiological withdrawal symptoms contribute indirectly, if at all, to the motivation to drink; preventing or diminishing acute withdrawal is not sufficient to prevent relapse. Instead, the post-withdrawal period—characterized by anxiety, negative affect, sleep disturbances, anhedonia and dysphoria—is associated with heightened vulnerability to relapse and elevated drinking. This rodent study reveals the selective involvement of the kappa-opioid receptor in motivational post-withdrawal syndrome, not acute physiological syndrome, and lends support to its potential value as a medication target. (Kissler JL, Walker BM. Neuropsychopharmacology 2016;41,560-567)

Alcohol self-administration is attenuated by kappa opioid receptor antagonist nor-binaltorphimine (Nor-BNI) during acute withdrawal.

Physiological withdrawal score following Nor-BNI administration.
TLR2 AND TLR4 EXPRESSION AND INFLAMMATORY CYTOKINES ARE ALTERED IN THE AIRWAY EPITHELIUM OF THOSE WITH ALCOHOL USE DISORDERS

AUD patients have a far greater incidence of pneumonia than the general population. This study investigates alcohol’s modification of alveolar epithelial cells and the resulting change in the inflammatory state of the airways as a mechanism by which alcohol consumption disturbs pulmonary lines of defense. The authors report that toll-like receptor (TLR)-2 is up-regulated and TLR4 decreased in AUD subjects, compared to nonsmoking/non-AUD subjects, and correlated with their scores on the AUDIT. Interleukin (IL)-6 and IL-8 were also increased in bronchial washings from AUD subjects. The combination increases susceptibility to pneumonia. (Bailey KL et al. (2015) Alcohol Clin Exp Res. Sep;39(9):1691-7)

- TLR2 increases with increasing AUDIT score
- TLR4 decreases with increasing AUDIT score
SHORT- OR LONG-TERM HIGH FAT DIET FEEDING PLUS ACUTE ETHANOL BINGE SYNERGISTICALLY INDUCE STEATOHEPATITIS IN MICE: AN IMPORTANT ROLE FOR CXCL1

Obesity and alcohol consumption often coexist and work synergistically to promote steatohepatitis. Feeding mice a high fat diet (HFD) and acute ethanol synergistically induce acute liver inflammation/injury through the elevation of hepatic or serum free fatty acids and subsequent up-regulation of hepatic chemokine CXCL1 expression and promotion of hepatic neutrophil infiltration. *(Chang B et al. Hepatology 2015 Oct; 62(4):1070-85)*

Mechanisms underlying the synergistic effect of high fat diet (HFD) and acute ethanol binge on steatohepatitis
Alcohol use may accelerate HIV disease progression, but the plausible biological mechanisms have not been clearly elucidated. Unhealthy alcohol use was independently associated with a marker of monocyte activation (i.e., higher sCD14) that predicts mortality in treated HIV-infected individuals. Longitudinal research should examine whether unhealthy alcohol use predicts changes in sCD14 prior to and following antiretroviral therapy initiation. (Carrico AW et al. Alcohol Clin Exp Res. 2015 Dec;39(12):2422-6)

Table 1. Demographics, Cigarette Smoking, and Health Status Indicators by Alcohol Use Group (N = 169)

<table>
<thead>
<tr>
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<th>Abstinent (n = 48)</th>
<th>Lower risk drinking (n = 37)</th>
<th>Unhealthy drinking (n = 84)</th>
<th>p-Value</th>
</tr>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>32 (28, 39.5)</td>
<td>29 (25, 37)</td>
<td>35 (29, 42)</td>
<td>.09</td>
</tr>
<tr>
<td><strong>Time since HIV diagnosis (years)</strong></td>
<td>2.7 (0.6, 6.6)</td>
<td>0.4 (0.1, 4.9)</td>
<td>1.1 (0.1, 6.4)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Soluble CD14 (ng/ml)</strong></td>
<td>1,387.0 (435.2)</td>
<td>1,456.0 (554.2)</td>
<td>1,675.9 (652.9)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>IL-6 (pg/ml)</strong></td>
<td>1.68 (1.26)</td>
<td>2.85 (7.82)</td>
<td>3.01 (5.33)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>d-dimer (ng/ml)</strong></td>
<td>0.80 (0.73)</td>
<td>0.69 (0.60)</td>
<td>0.86 (1.48)</td>
<td>0.76</td>
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This study, a secondary analysis of two clinical trials for AUD, examined the associations between pain, negative affect, and AUD treatment outcomes. Pain scores were associated with drinking outcomes in both datasets. Pain scores were also positively associated with negative affect, and negative affect mediated the association between pain and drinking outcomes. Social behavior network therapy attenuated the association between pain and drinking. (Witkiewitz et al. J. Consul Clin Psychol, 83(6):1044-1057)

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<th>UKATT</th>
<th>B (SE; 95% CI)</th>
<th>R²</th>
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<tr>
<td>12-month % Drinking Days (PDD) (RMSEA=0.08 (90% CI: 0.06, 0.09), CFI = 0.96)</td>
<td>0.008 (.002; 95% CI: .004, .012) *</td>
<td>.19</td>
</tr>
<tr>
<td>Pain slope → Affect slope → PDD Mediation</td>
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<tr>
<td>12-month Drinks/Drinking Day (DDD) (RMSEA=0.08 (90% CI: 0.06, 0.09), CFI = 0.96)</td>
<td>0.002 (.001; 95% CI: .001, .004) *</td>
<td>.29</td>
</tr>
<tr>
<td>Pain slope → Affect slope → DDD Mediation</td>
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<tr>
<td>12-month % Heavy Drinking Days (PHDD) (RMSEA=0.08 (90% CI: 0.06, 0.09), CFI = .96)</td>
<td>0.009 (.002; 95% CI: .005, .01) **</td>
<td>.23</td>
</tr>
<tr>
<td>Pain slope → Affect slope → PHDD Mediation</td>
<td></td>
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<tr>
<td>12-month Maximum Drinks/Day (MXD) (RMSEA=0.08 (90% CI: 0.06, 0.09), CFI = .96)</td>
<td>0.003 (.001; 95% CI: .001, .01) **</td>
<td>.27</td>
</tr>
<tr>
<td>Pain slope → Affect slope → MXD Mediation</td>
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This paper provides a perspective on how translational research on stress-related mental disorders is being powered by an ever-developing appreciation of the shared neural circuits and genetic architecture that moderate the response to stress across species. It also addresses research approaches that have the potential to deliver a new generation of risk biomarkers and therapeutic strategies for stress-related disorders. (Hariri A, Holmes A. Nature Neuroscience 2015 Oct;18(10):1347-52)
FINDING TRANSLATION IN STRESS RESEARCH

1970s
- Benzodiazepines discovered, spawning the psychopharmacology era
- Study of ethology and species-specific defensive behaviors

1980s
- Diagnostic categorizations cement shift from ‘neurosis’ to anxiety disorders
- Rodent conditioned fear tests used to find neural loci of ‘anxiety’
- Fluoxetine and other SSRIs rapidly adopted as anxiolytic drugs
- Human association studies report genes related to anxiety
- Buspirone approved as alternative to benzodiazepines

1990s
- Big Five personality structure includes the trait ‘neuroticism’
- Rodent assays for ‘anxiety’ (e.g., EPM, LD) widely employed
- New tools for genetic manipulations spur mouse models of anxiety
- Human amygdala responses to threat measured

2000s
- Trauma- or stressor-related disorders split from anxiety disorders
- Extinction widely employed as a translational assay
FINDING TRANSLATION IN STRESS RESEARCH

- RDoC promote mechanistic and dimensional diagnoses
- Invasive neural manipulations (e.g., DBS) used therapeutically
- Robust genetic risk factors for trauma & anxiety disorders
- Reliable biomarkers of risk become part of routine clinical practice
- New tools for precision control & visualization of rodent brain in vivo
- New, efficacious anxiolytic drugs developed
- Technological advances in cognitive-behavior therapy
- Non-invasive neural manipulations (e.g., rTMS) used therapeutically

Marina Corral Spence/Nature Publishing Group
MANAGEMENT OF ALCOHOL USE DISORDER IN PATIENTS REQUIRING LIVER TRANSPLANT

• This paper critically reviews and discusses the clinical, public health, and bioethical issues related to the treatment of AUD before and after liver transplant.

• AUD is the second most common cause of liver transplant.

• Treatments for alcoholic liver disease are limited, and the management of patients with AUD who require liver transplant may be challenging.

• Provision of integrated psychosocial and pharmacological treatment administered by addiction specialists who are members of the transplant team is needed and recommended.

• An integrated team approach, use of comprehensive contextual evaluation of substance use, and behavioral, psychosocial, and pharmacologic interventions before transplant optimize outcomes in AUD patients.

(Lee MR, Leggio L. Amer J of Psych, 2015 Dec 1;172(12):1182-9)
CAN A CRIMINAL JUSTICE ALCOHOL ABSTENTION PROGRAMME WITH SWIFT, CERTAIN, AND MODERATE SANCTIONS (24/7 SOBRIETY) REDUCE POPULATION MORTALITY?

A RETROSPECTIVE OBSERVATIONAL STUDY

A rigorous evaluation of the 24/7 sobriety program for alcohol-involved offenders in South Dakota found the program was linked to a surprisingly large (4.2%) reduction in all-cause mortality. These findings, drawn from a strong statistical design, suggest but do not show that the program has spillover effects on members of the population who are not enrolled in the program. (Nicosia N, Kilmer B, Heaton P. The Lancet Psychiatry 2016. To Be Published Online, February 2016)

All cause mortality before and after 24/7 program implementation
SEX DIFFERENCES IN ANIMAL MODELS: FOCUS ON ADDICTION

- This review addresses sex differences in preclinical animal models of addiction.

- Female rats, in general, acquire the self-administration of drugs and alcohol more rapidly, escalate their drug taking with extended access more rapidly, and show more motivational withdrawal and greater reinstatement.

- The one exception is that female rats show less motivational withdrawal from alcohol.

- These sex differences appear to be both organizational (i.e., estradiol treated neonatal animals show the male phenotype), and activational (i.e., female phenotype depends on the effects of gonadal hormones).

- Differences within the estrous cycle are relatively minor: most prevalent during acquisition of drug taking; less influential once compulsive drug taking is established.

- A better understanding of how males and females differ will help scientists design experiments to characterize sex differences in new phenomena under investigation.

This study used NSDUH data to explore changes in alcohol use and associated outcomes among females and males aged 12+ between 2002-2012.

Although men still drink more than women, differences in drinking patterns narrowed for current drinking, number of drinking days per month, past year DSM-IV alcohol abuse, and past-year driving under the influence of alcohol.

Average number of drinking days and the percentage of people who drank in the previous 30 days increased for females and decreased for males.

Among 18-25 year olds not in college, binge drinking increased among women, but decreased among men.

The evidence of increasing alcohol use by women is particularly concerning given that women are at greater risk of a variety of alcohol-related health effects, including liver inflammation, cardiovascular disease, neurotoxicity, and cancer.

White A, Castle IJ, Chen CM, Shirley M, Roach D, Hingson R. Alcohol Clin Exp Res. 2015 Sep;39(9):1712-26
This study assessed the effectiveness of a web-based, combined sexual assault risk and alcohol use reduction program for college women. For women with a history of sexual assault, participating in the program reduced sexual assault risk and heavy episodic drinking. The combined intervention was only effective in reducing sexual re-assault rates and not first sexual assault experiences. Web-based personalized feedback programs targeting sexual assault may be a cost effective option for reducing sexual assault and heavy episodic drinking on college campuses. (Gilmore AK, Lewis MA, George WH. Behav Res Ther. 2015 Nov;74:38-49)

Interaction of combined sexual assault/drinking reduction program (combined) and alcohol-related sexual assault (ASA) incidence and severity.
THANK YOU!

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