135th Meeting of the NATIONAL ADVISORY COUNCIL ON ALCOHOL ABUSE AND ALCOHOLISM

February 5, 2014

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National Institutes of Health
The total FY 2013 appropriation for NIAAA was $433.4 million.

Within this appropriation, NIAAA awarded 648 research project grants (RPGs), including 166 competing awards, which corresponds to a success rate of 20%.

FY 2013 support levels for other key extramural funding mechanisms included:

- 18 research centers for $26.0 million
- 135 other research grants for $35.0 million
- 270 full-time training positions for $11.4 million
- $37.6 million for research and development contracts
After a lengthy continuing resolution, the Consolidated Appropriation Act, 2014 (H.R. 3547) was signed by the President on January 17th. NIH received a total of $29.9 billion, $1 billion above the fiscal year 2013 post-sequestration level.

The FY 2014 appropriation for NIAAA provides $444.9 million.

This represents a $11.5 million or a 2.7% increase over the FY 2013 post-sequestration budget level.

NIAAA estimates it will support a total of 652 RPGs in FY 2014, including 175 competing awards.
NIAAA Budget

FY 2015

• Preliminary work on the budget for FY 2015 is beginning.

• After intermediate stages of review, the President’s budget request for FY 2015 will be presented to Congress on March 3, 2014, at which time it will become available to the public.
New Staff

Nancy Diazgranados, M.D., M.Sc., joins the Section of Clinical Assessment & Treatment Evaluation as a Staff Clinician. Her current work is in clinical research, mood disorders, clinical pharmacology, and experimental therapeutics.

Dr. Diazgranados received her doctoral degree in Medicine and Surgery from the Pontificia Universidad Javeriana in Bogota Colombia. She completed her Psychiatry residency at Albert Einstein Medical Center and received a Master in Science degree in Pharmacology from Thomas Jefferson University.
Bonnie L. Ellis joins the Administrative Services Branch as a Section Chief, Administrative Officer.

She has been with the National Institutes of Health for 24 years, 17 of which were spent at the Center for Scientific Review (CSR) and seven with the Office of the Director. Her last position before joining NIAAA was an Administrative Officer at CSR. In her current position, she will support the Office of the Director and Extramural Research.
Honors & Awards

• **Dr. Abraham Bautista**, Director of the Office of Extramural Activities, received the 2013 Leadership Excellence Award from the NIH Asian Pacific Islander American Organization for exhibiting leadership excellence, mentorship, empowerment of Asian and Pacific Americans to promote diversity, and support of the overall mission of NIH.

• **Dr. Ralph Hingson**, Director of the Division of Epidemiology and Prevention Research, received the University of Pittsburgh Legacy Laureate Award on September 27, 2013. The University of Pittsburgh gives this award to alumni recognized for their outstanding professional and personal accomplishments.
Honors & Awards

• **Dr. Lorenzo Leggio**, Chief of the joint NIAAA-NIDA Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology (CPN), Laboratory of Clinical and Translational Studies (LCTS), was appointed as Editor-in-Chief for North America for *Alcohol and Alcoholism*, the official journal of the European Society for Biomedical Research on Alcoholism (ESBRA).

• **Dr. Lorenzo Leggio**, together with Dr. Fatemeh Akhlaghi from the University of Rhode Island, received one of the nine NCATS grant awards of the “Discovering New Therapeutic Uses for Existing Molecules” initiative. This is a translational project that will look at the effects of a ghrelin receptor antagonism in alcoholism. The project involves the NIH Intramural Research Program (NIAAA/LCTS, NIDA IRP, CC), the NIA Extramural Programs (NCATS and NIAAA), the University of Rhode Island, and Pfizer.
Honors & Awards

• Dr. Mary Lee and Dr. Lorenzo Leggio, respectively Staff Clinician and Chief at the joint NIAAA-NIDA Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology (CPN), LCTS, received one of the “Bench-to-Bedside” (B2B) grant award selected for funding in the behavioral and social sciences category. This is a translational project that will look at the effects of oxytocin in alcoholism. The project involves the NIH Intramural Research Program, i.e., NIAAA/LCTS, NIDA IRP, NIAAA/LNI, NIMH, and CC.

• Dr. Cheryl Marietta, a Senior Research Assistant in the Laboratory of Neurogenetics and the lab’s safety guru, won an “NIH Mission First, Safety Always” award.

This study shows that chronic intermittent ethanol exposure facilitates forms of rewarded learning known to be mediated by the dorsolateral striatum, suggest a possible route by which alcohol abuse may prime striatal circuits to acquire information about reward related stimuli and set the stage for stimulus-controlled behaviors.

• **Cannabinoid Receptor Mediating Compounds.** (Kunos G, Iyer MR, Cinar R, Rice KR. PCT patent application No. PCT/US2013/069686)

An intramural group developed and patented a new class of dual-action drugs which, in addition to blocking CB1 receptors outside of the brain, also inhibit iNOS or activate AMPK. The prototype CB1R/iNOS dual inhibitor displayed improved antifibrotic activity over single target compounds in a mouse model of liver fibrosis.

This study shows that a dysfunctional (stop codon) form of the gene encoding the metabotropic glutamate receptor 2 (Grm2) in P but not in NP rats, and that genetic deletion or pharmacological blockade of Grm2 increased alcohol consumption in normal rats and mice.


This study shows that increasing the tissue levels of the endogenous cannabinoid anandamide in the amygdala – a brain region associated with fear – reduces fear reactions in mice by facilitating the extinction of learned fear, and in parallel studies, people who carry a low-expressing variant of the FAAH gene exhibited quicker habituation of amygdala reactivity to threat, as documented by brain imaging.

This study suggests an impaired protective response, the absence of FOXO3a, to explain the progression of ALD to a more severe clinical phenotype in a small minority of those who drink heavily.


The combination of HCV and alcohol, but not either condition alone, inactivates FOXO3, causing decreased expression of target genes and an increase in liver injury. Modulation of the FOXO3 pathway is a potential therapeutic approach for HCV-alcohol-induced liver injury.


This study demonstrates a variable immune response in heavy vs moderate drinking macaques as a possible explanation for one of the health benefits ascribed to moderate use of alcohol in reducing risk of cold and other viral infections.

This study shows that the placebo effect varies significantly across trials but was negatively correlated with treatment effect size.


This study shows that individuals with substance abuse-related medical conditions benefit from integrated medical and substance abuse treatment, and such an approach may be cost effective.

This study shows that varenicline, the nicotine partial agonist, significantly reduced alcohol consumption and craving in a double-blind, placebo-controlled trial for alcohol dependence.


This study shows that gabapentin was effective in treating alcohol dependence and relapse-related symptoms of insomnia, dysphoria and craving with a favorable safety profile in a double-blind, placebo-controlled trial randomized dose-ranging trial.

This study shows that knock-in mice expressing ethanol resistant NMDA receptors drank more ethanol in an intermittent 24h access paradigm supporting the hypothesis that NMDA receptors may mediate a “stop” drinking signal.


This study shows that reconsolidation of alcohol-related memories activates the mammalian target of rapamycin complex 1 (mTORC1) in select regions of the amygdala and cortex.

This study shows that massive aberrations in intra-neocortical connections following prenatal alcohol exposure.


These results show significantly lower blood flow in the insula cortex in alcohol-dependent men that could mediate deficits in switching between functional networks that translate to problems in inhibitory control.

This report reviews underage drinking and related traffic fatality trends and new research on social determinants, consequences, and prevention interventions published since the 2007 Surgeon General’s Call to Action to Prevent and Reduce Underage Drinking.


This article discusses the implication of findings from a Monitoring the Future study that will be published in the same issue of JAMA Pediatrics” by Megan Patrick et al. showing that, between 2005 and 2011, the percentages of high school seniors nationwide who binge drink (5 or more drinks per occasion) have declined but not the percentages who consume 15 or more drinks per occasion.


This study shows that in a large national survey, Americans had poorer diets on days they drank.

This study found differences in subjective effects of alcohol between high- and low-risk drinkers, notably greater levels of stimulation immediately after drinking alcohol, and greater sedation during a subsequent stress period than social drinkers.
Stages of the Addiction Cycle

- **Preoccupation with obtaining**
  - Persistent physical/psychological problems

- **Persistently desire**
  - Larger amounts taken than expected

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**ADDITION**

- **Tolerance**
- **Withdrawal**
  - Negative Affect
  - Compromised social, occupational, or recreational activities
- **Binge Intoxication**
Theoretical Framework Relating Addiction Cycle to Motivation for Drug Seeking

Positive and Negative Reinforcement - Definitions

**Positive Reinforcement** — defined as the process by which presentation of a stimulus (drug) increases the probability of a response (nondependent drug taking paradigms).

**Negative Reinforcement** — defined as a process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (dependence-induced drug taking).
Neurobiology of Addiction

From: Koob GF, Volkow ND
Bottom Line

1. Addiction is an incentive salience disorder

2. Addiction is a reward deficit disorder

3. Addiction is a stress surfeit disorder

4. Addiction is an executive function disorder
Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity

Experimental design: tissue collected following extinction training and/or AM3506 (FAAH inhibitor) treatment

Extinction training (= ‘CS-US’) and AM3506, increased anandamide levels in amygdala

Gunduz-Cinar, MacPherson… Holmes et al 2013 Molecular Psychiatry 18:813-823
Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity

AA carriers have less FAAH activity (and presumably more brain anandamide).

Amygdala of AA more rapidly habituation to a fearful stimulus.

AA score low on Stress Reactivity Trait, Predicts reduced vulnerability to PTSD.

‘My feelings are hurt rather easily’
‘I am too sensitive for my own good’

Gunduz-Cinar, MacPherson...
Holmes et al 2013 Molecular Psychiatry 18:813-823
Koob Goals for NIAAA

1. Understand the unique molecular-cellular actions of alcohol

2. Understand the neuroplasticity of neurocircuits that drive excessive drinking and alcoholism

3. Develop evidence based prevention and treatment for excessive drinking and alcoholism across the developmental spectrum from the fetus to old age

4. Understand the role of alcohol in organ pathology and develop effective prevention and treatment strategies for such pathology

5. Increase understanding of the epidemiology and underpinnings of underage drinking and how the problems of underage drinking and high risk college drinking can be effectively addressed.

6. Develop improved approaches for the delivery of health services for alcohol disorders.

7. Promote and recruit young investigators to the alcohol field, promote and recruit women to the alcohol field, promote and recruit minorities to the alcohol field