

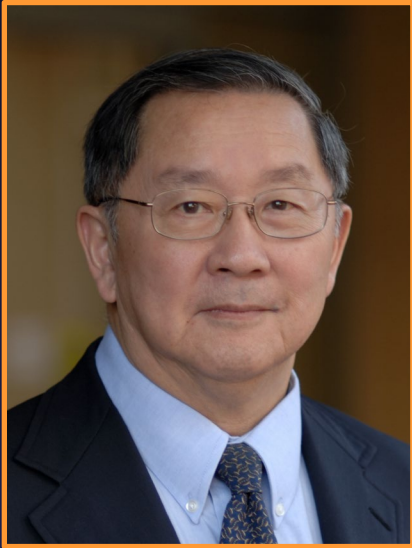
**NIAAA DIRECTOR'S REPORT
ON INSTITUTE ACTIVITIES TO THE 150TH MEETING
OF THE NATIONAL ADVISORY COUNCIL ON
ALCOHOL ABUSE AND ALCOHOLISM**

**FEBRUARY 7, 2019
BETHESDA, MD**

**George F. Koob, Ph.D.
Director**

**National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health**

In Memoriam



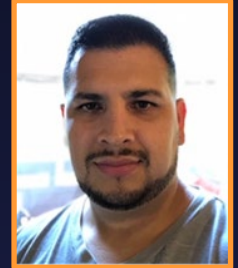
Ting-Kai Li, MD, a renowned scientist who served as NIAAA's director from 2002 to 2008, passed away on November 18, 2018.

As NIAAA Director, Dr. Li provided visionary leadership, blending administrative expertise with a comprehensive understanding of alcohol's impact at the metabolic, neurobiological, clinical, epidemiological, and societal levels.

His legacy will live on in his work and contributions to the alcohol field.

Welcome to New NIAAA Staff

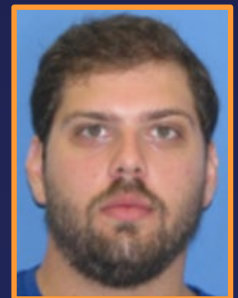
Carlos Gomez joined the Administrative Services Branch, Office of Resource Management, as an Administrative Officer supporting the extramural offices and divisions within NIAAA. He previously served as an Administrative Officer in the NIH Office of the Director.



Dr. Kari Johnson joined the intramural program's Laboratory for Integrative Neuroscience as a Research Fellow after completing a Postdoctoral Research Associate Training (PRAT) fellowship. She received her PhD in pharmacology from Vanderbilt University.



Dr. Andrew Kesner joined the Laboratory for Integrative Neurosciences as a Postdoctoral Fellow. Dr. Kesner received his PhD from Johns Hopkins University as part of the Graduate Partnership Program with the National Institute on Drug Abuse.



Welcome to New NIAAA Staff

Dr. Daniel Liput joined the Laboratory for Integrative Neuroscience as a Research Fellow after completing his Intramural Research Training Award (IRTA) fellowship. He received his PhD in neuroscience from the University of Kentucky.



Dr. Aya Matsui joined the Laboratory on the Neurobiology of Compulsive Behavior as a Research Fellow. Dr. Matsui received her PhD in neuroscience from the Vollum Institute at Oregon Health and Science University.



Dr. Benson Stevens joined the Section on Human Psychopharmacology (SHP) as a Postdoctoral Fellow. Dr. Stevens received his PhD in neuroscience from Georgetown University.



Welcome to New NIAAA Staff

Dr. Dominique Lorang-Leins joined the Division of Neuroscience and Behavior as a Program Director for Extramural Basic Research. She previously served as a Scientific Review Officer in the Genes, Genomes, and Genetics Integrated Review Group at the NIH Center for Scientific Review (CSR).



Dr. Jenica Patterson joined the Division of Neuroscience and Behavior as a Program Officer for Extramural Research. She was previously a Senior Program Manager at ECS Federal where she provided technical expertise and programmatic support at the Defense Advance Research Program Agency (DARPA).



Welcome to New NIAAA Staff

Samara Toussaint, MPH, joined the Division of Epidemiology and Prevention Research as a Program Analyst. She previously worked as an Improvement Specialist at University Research Co., LLC, and as an Associate Program Manager at Population Services International.



Dr. Pamela Wernett joined the Science Policy Branch as a Senior Health Science Policy Analyst. She previously worked in the Office of Science Policy within the NIH Office of the Director, where she served as a Health Science Policy Analyst in the Clinical and Healthcare Research Policy Division.



NIAAA Staff Transitions

Internal Transitions

Daniel Smyth joined the Ethics and Management Analysis Branch, Office of Resource Management, as a Management Analyst. Dan was previously a Program Analyst in the Division of Epidemiology and Prevention Research.



Departing Staff

Shuly Babitz, Public Liaison Specialist and Writer/Editor for the Communications and Public Liaison Branch, transferred to the Maternal and Child Health Bureau, Health Resources Services Administration as a Health Communications Strategist.



Dr. Jennifer Hobin, Chief, Science Policy Branch, transferred to the National Institute on Drug Abuse where she now serves as Deputy Director of the Office of Science Policy and Communications.



Dr. Roz Breslow retired from the Division of Epidemiology and Prevention Research (DEPR) in December 2018 after 17 years of service as an epidemiologist.



NIAAA Staff Transitions

Departing Staff

Dr. Marcia Scott retired from the Division of Epidemiology and Prevention Research (DEPR) in December 2018 after 16 years of service as a Health Scientist Administrator.



Dr. Karina Possa Abrahao, Research Fellow, departed the Laboratory for Integrative Neuroscience to become an Assistant Professor at the Departamento de Psicobiologia, Universidade Federal de São Paulo.



Dr. Andrea Barnes, Chief, Office of Laboratory Animal Science, retired after 10 years of service at NIAAA and 33 years of government service.



FY 2019 Budget

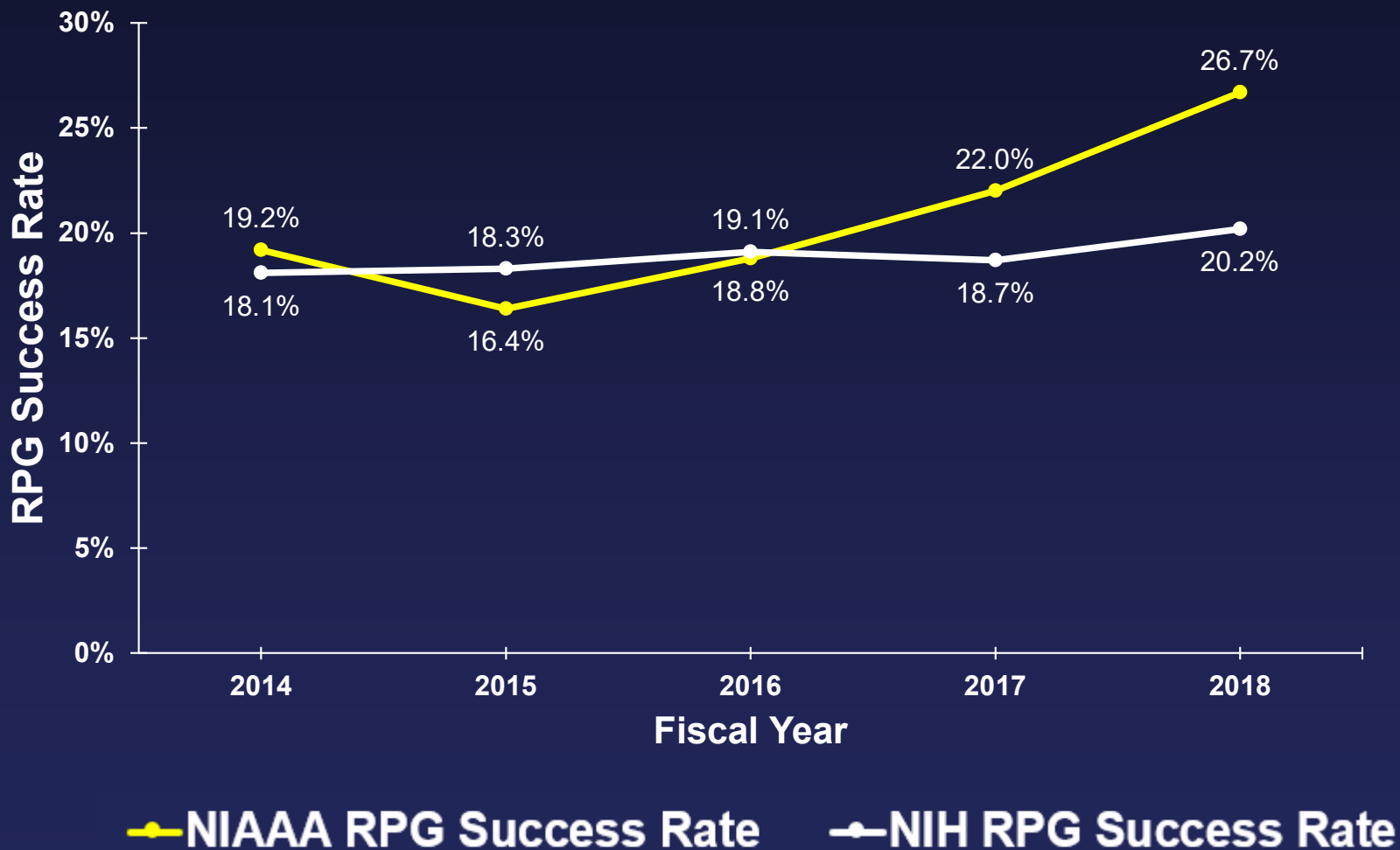
- NIAAA closed out the FY 2018 budget (\$509.6 million)
- NIH received a total of **\$39.3 billion** for FY 2019, including:
 - General increases for NIH institutes and Centers
 - Ongoing support for the Gabriella Miller Kids First Act pediatric research initiative
 - Allocations for research on opioids, the 21st Century Cures Act, the BRAIN Initiative, and research on influenza
- NIAAA received a total of **\$525.6 million** for FY 2019

FY 2018 Budget Closeout

FY 2018 Budget	
NIH	\$37.2 billion
NIAAA	\$509.6 million
Research Project Grants	738
Competing Awards	253
Other Research Grants	175
Research Centers	20
Training Positions	305
Research and Development Contracts	\$34.4 million

Good News: NIAAA Success Rates 2014-2018

NIAAA & NIH RPG Success Rates 2014-2018



Funding Opportunity Announcements (FOAs)

New NIAAA FOAs

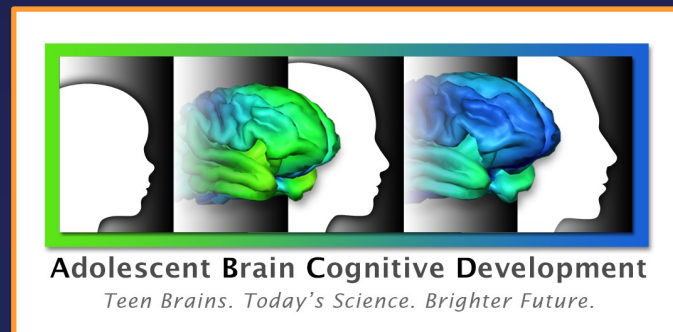
- Collaborative Study on the Genetics of Alcoholism (U10)
- Alcohol-HIV/AIDS Program Project (P01)
- Comprehensive Alcohol-HIV/AIDS Research Center (P60)
- Specialized Alcohol Research Centers Clinical Trial Optional (P50)
- Medications Development for the Treatment of Alcohol Use Disorder (U01)
- Summer Research Education Experience Program (R25)

New NIH-wide FOAs with NIAAA participation

- Over 40 current funding opportunities, including:
 - 17 HEAL Initiative RFAs
 - 6 BRAIN Initiative RFAs

Collaborative Research on Addiction at NIH (CRAN)

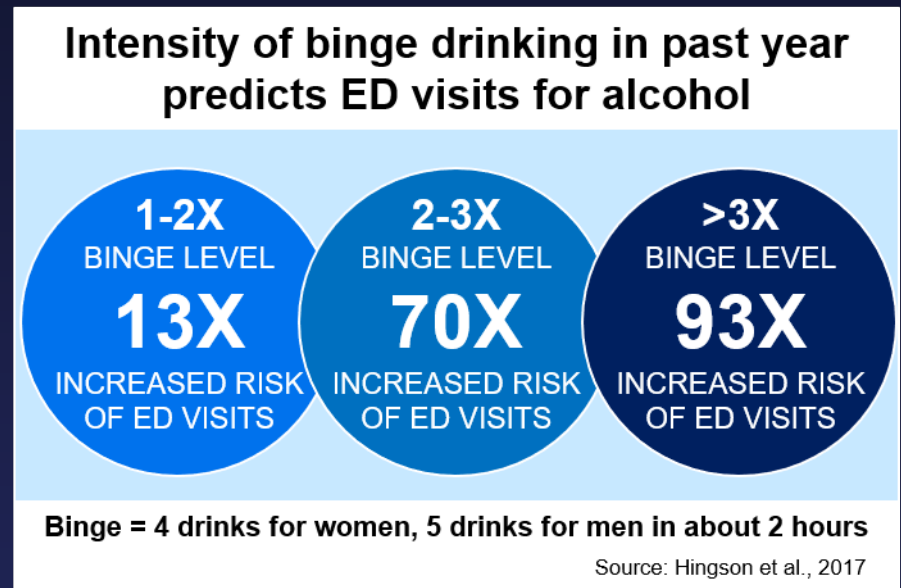
- **Adolescent Brain Cognitive Development (ABCD) Study**
 - Baseline recruitment is complete: 11,874 participants (ages 9-10) enrolled
 - The focus will now shift to retention of the enrolled participants as they progress through adolescence
- Three NIH Notices were released in October describing an intent to publish limited-competition funding opportunity announcements (FOAs) for renewal of the Coordinating Center, the Data Analysis and Informatics Center, and the Research Project Sites of the nationwide ABCD Consortium.



Response to an Emerging Issue: High Intensity Drinking

High-Intensity Drinking: alcohol intake at levels twice or more the threshold for binge drinking (predictive of increased harm)

- In October, NIAAA convened a **working group** of external experts to better understand the **social and cultural** determinants of **high-intensity drinking** to inform the development of improved interventions.
- The panel consisted of experts in alcohol and drug policy, neuroscience, digital media, social media analysis, adolescent alcohol intervention research, and global health.



A meeting summary is available on the NIAAA website.

NIAAA Outreach

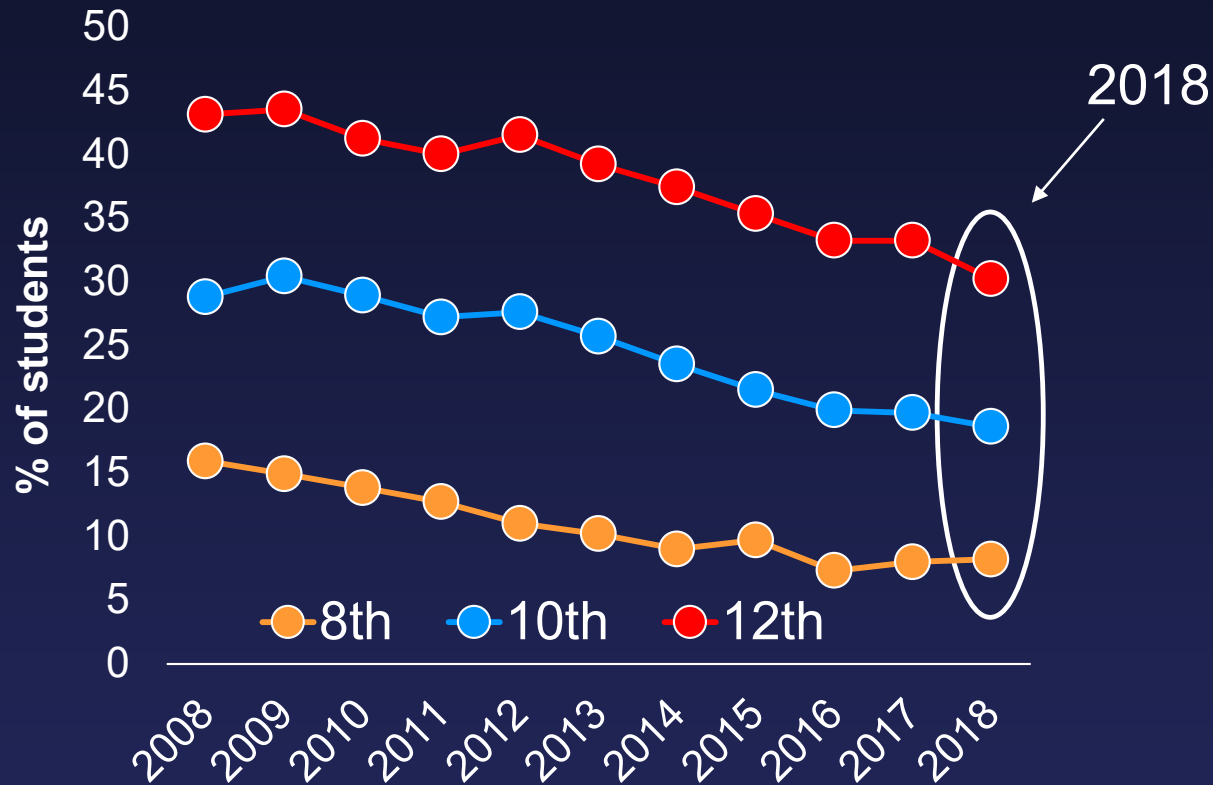
- NIAAA and the Community Anti-Drug Coalitions of America (CADCA) co-sponsored a screening of the HBO documentary “**Risky Drinking**” in Washington, DC last September, followed by a Q & A session.
- NIAAA continues to be active in alcohol-related Twitter chats:
 - In recognition of **National Fetal Alcohol Spectrum Disorders Awareness Day**, NIAAA partnered with the National Organization on Fetal Alcohol Syndrome (NOFAS) in a September 2018 Twitter chat.
 - In October 2018, NIAAA hosted an **#AlcoholYouthChat** with the American Society of Addiction Medicine (ASAM) on recognizing and preventing underage drinking.
- In January 2019, NIAAA participated in **National Drugs and Alcohol Chat Day**, an annual live online chat between high school students and NIH scientists



@NIAAAnews

Good News: Success in Reducing Underage Drinking

Alcohol use past 30 days



Percentage of teens who drink decreased by one-third in the past decade

Priority: Support Dissemination and Implementation of Evidence-based Prevention Resources

In Development: Core Prevention Resource

- **The CPR is envisioned as a easy-to-use online resource that specifically distills and synthesizes underage drinking preventive interventions into five prevention domains (i.e., individual, family, school, community, and policy)**
- **Preventive interventions for underage drinking shared via the CPR will be applicable to school and community settings, with a focus on effective school-based interventions**

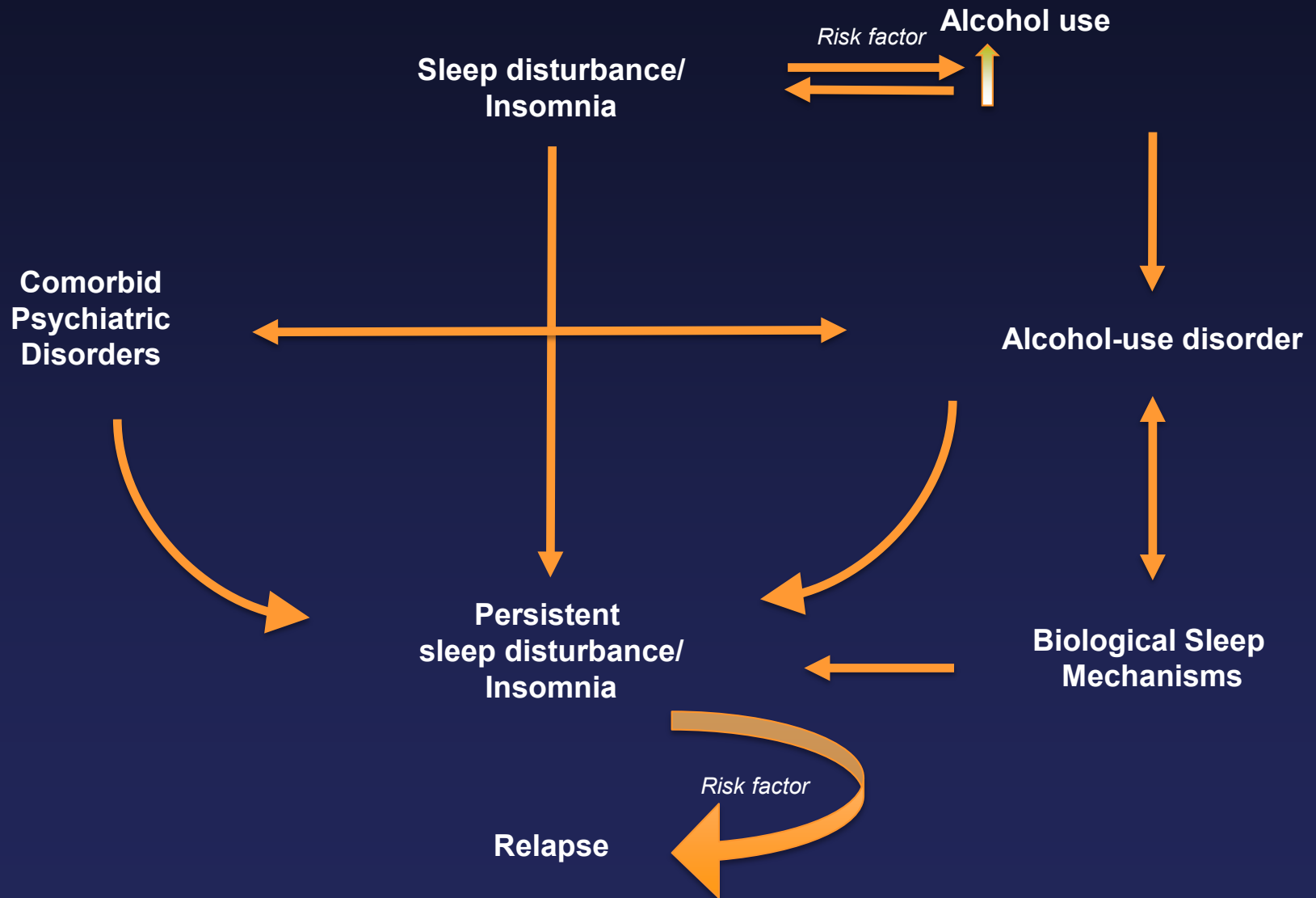
In Development: “Clinician’s Navigator”

- **Expanding reach beyond patients/families**
- **Resource for health professionals: General practice physicians, nurses, social workers, employee assistance professionals, etc.**
 - **How to build a “rolodex” of local treatment providers**
 - **Provider directories, signs of quality, etc.**
 - **How to teach patients to use the Treatment Navigator**
 - **Talking points, video walkthrough, brochure**

In Development: NIAAA Clinician's Toolkit

- **What every clinician needs to know about alcohol**
 - Presentation in primary care
 - Role in common co-occurring conditions
 - Neuroscience
 - Alcohol misuse across the lifespan
 - Diagnostic criteria, recommended drinking limits
 - Alcohol withdrawal syndrome
 - Evidence-based therapies/medications
 - Addressing stigma
 - Interactions with commonly used medications
- **Suggestions for practice**
 - How to start the conversation
 - Clinician's Guide, Screening Tools, Rethinking Drinking, etc.

Emerging Issue: Sleep and Alcohol Use Disorder: A Two Way Interaction



Emerging Issue: Alcohol Misuse Causes Pain and Pain Causes Alcohol Misuse

16-25% chronic pain patients drink heavily or have AUD

K Witkiewitz & KE Vowles (2018) Alcohol Clin Exp Res

43%-73% of individuals with AUD have moderate to severe pain

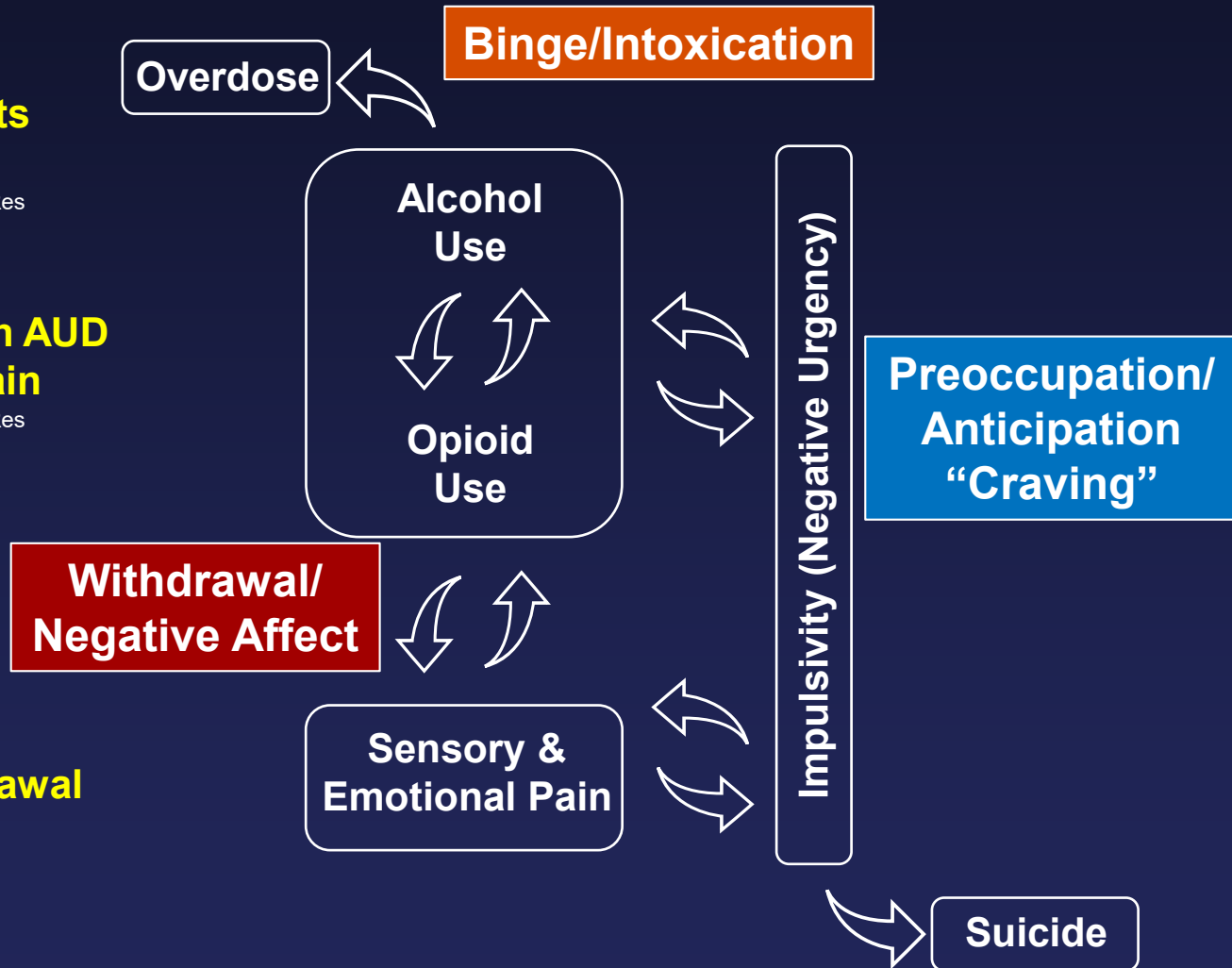
K Witkiewitz & KE Vowles (2018) Alcohol Clin Exp Res

Acute alcohol (at binge levels) is analgesic (relieves pain)

T Thompson et al. (2017) Journal of Pain

Chronic alcohol and withdrawal produce hyperalgesia (increased pain sensitivity)

S Edwards et al. (2012) Neuropharmacology



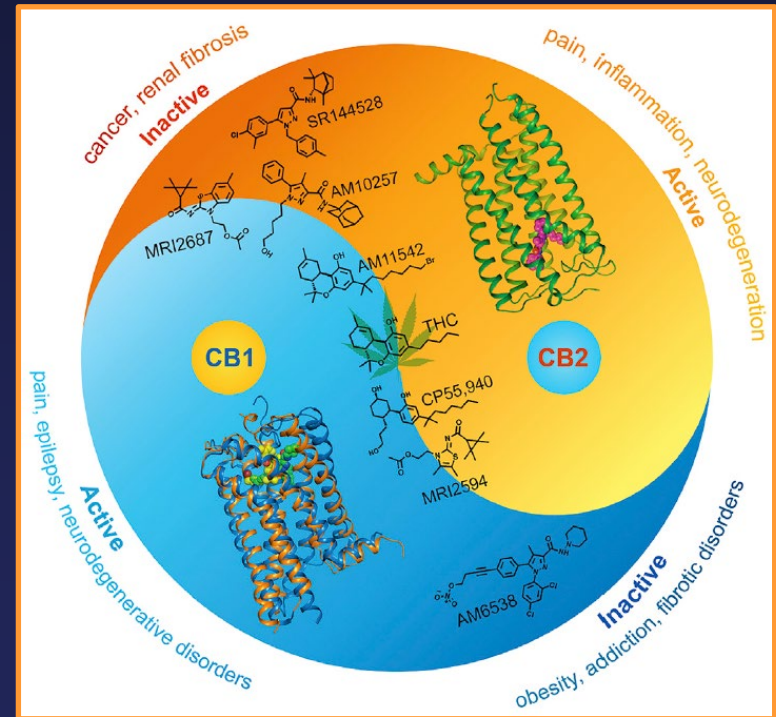
Research Highlights

Crystal Structure of the Human Cannabinoid Receptor CB2

The cannabinoid receptor CB2 has therapeutic potential for neuropathic pain, inflammation, and neurodegenerative disorders.

The current study describes the crystal structure of the antagonist-bound human CB2 receptor and provides important insight into the activation mechanisms of the CB2 receptor. These findings could facilitate the rational design of novel therapeutic drugs targeting cannabinoid receptors.

- **Crystal structure of human CB2 in complex with antagonist AM10257 is determined**
- **A high degree of conformational similarity with the agonist-bound CB1 is uncovered**
- **The yin-yang relationship of CB2 and CB1 will facilitate the design of selective drugs**

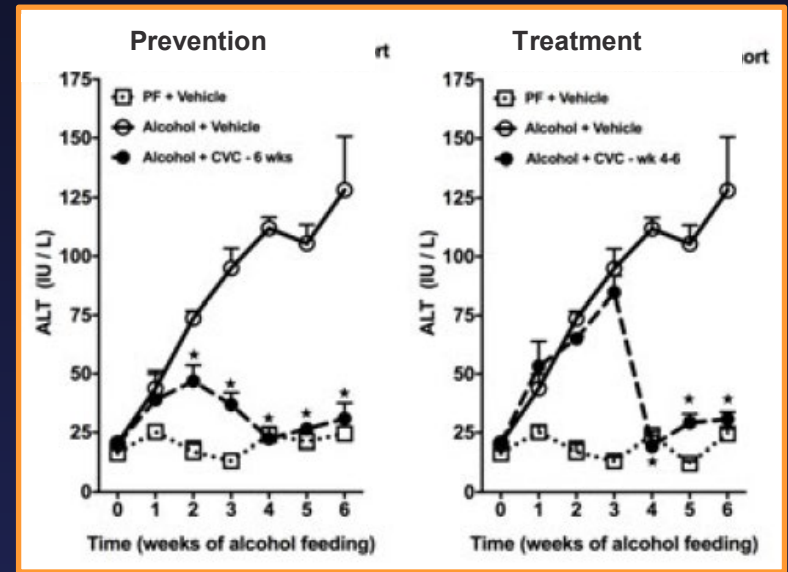


Pharmacological Inhibition of CCR2/5 Signaling Prevents and Reverses Alcohol-Induced Liver Damage, Steatosis and Inflammation in Mice

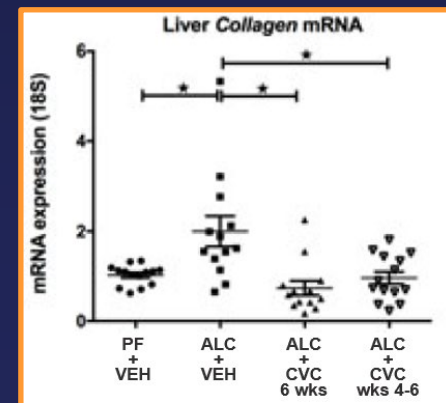
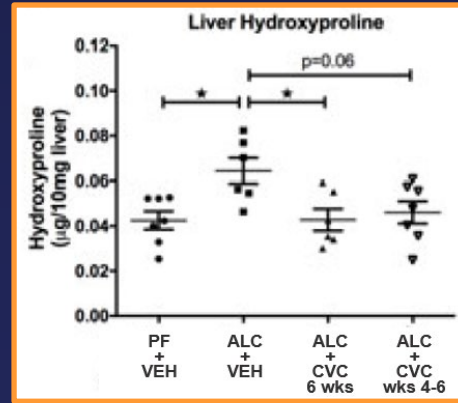
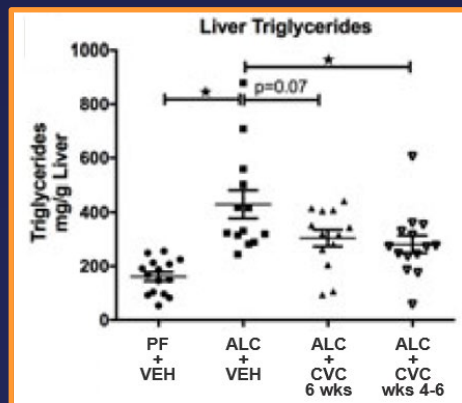
A prominent pathology of alcoholic hepatitis is liver infiltration by immune cells which requires chemokine receptors CCR2 and CCR5.

The current study tested a dual CCR2-CCR5 inhibitor, cenicriviroc (CVC), in a mouse model of alcohol-associated liver disease and found that CVC was highly effective in both preventing and reversing liver injury, including inflammation, fibrosis, and cell death. The current study provides preclinical evidence that CVC might be clinically effective against alcoholic hepatitis.

CVC both prevented and reversed alcohol-induced ALT elevations (a marker for liver injury)



CVC both prevented and reversed markers of liver steatosis and fibrosis

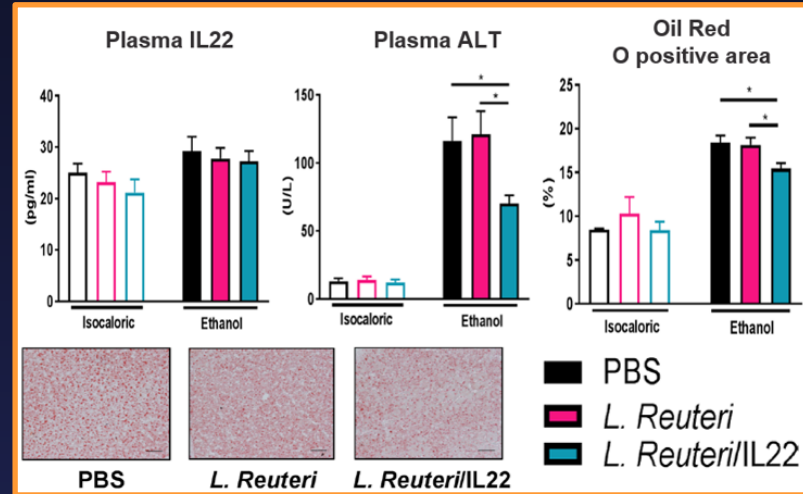


Bacteria Engineered to Produce IL-22 in Intestine Induce Expression of REG3g to Reduce Ethanol-Induced Liver Disease in Mice

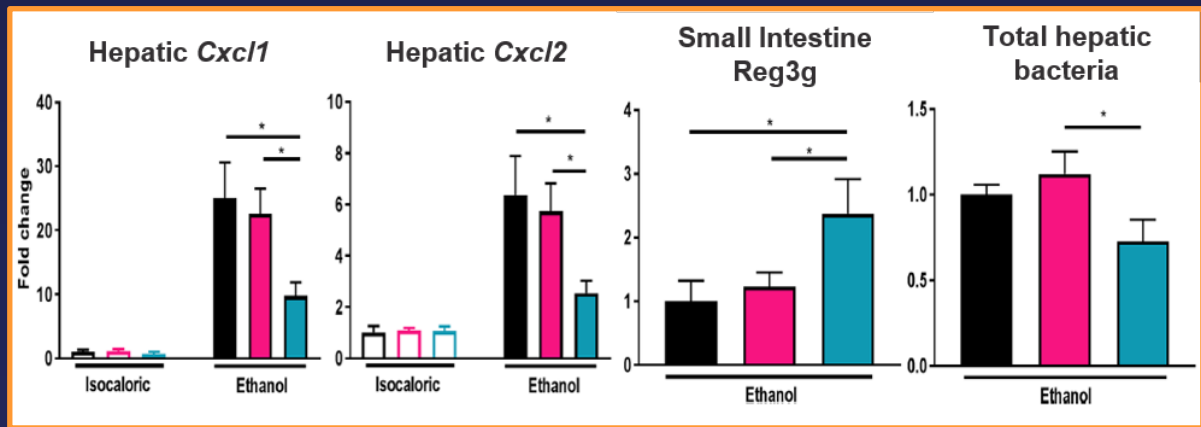
Alcohol-induced dysbiosis and gut barrier dysfunction in mouse models have been linked to a reduced expression of the cytokine interleukin 22 (IL-22) and its downstream effector, regenerating islet-derived 3 gamma (REG3G), an antibacterial protein.

The current study identifies the underlying mechanism of IL-22 and REG3g suppression in a mouse model of alcohol-associated liver disease and demonstrates that alcohol-induced liver damage can be reduced by introduction of bacteria engineered to produce IL-22.

Administration of *L. reuteri*/IL-22 significantly reduced steatohepatitis without influencing circulating IL-22



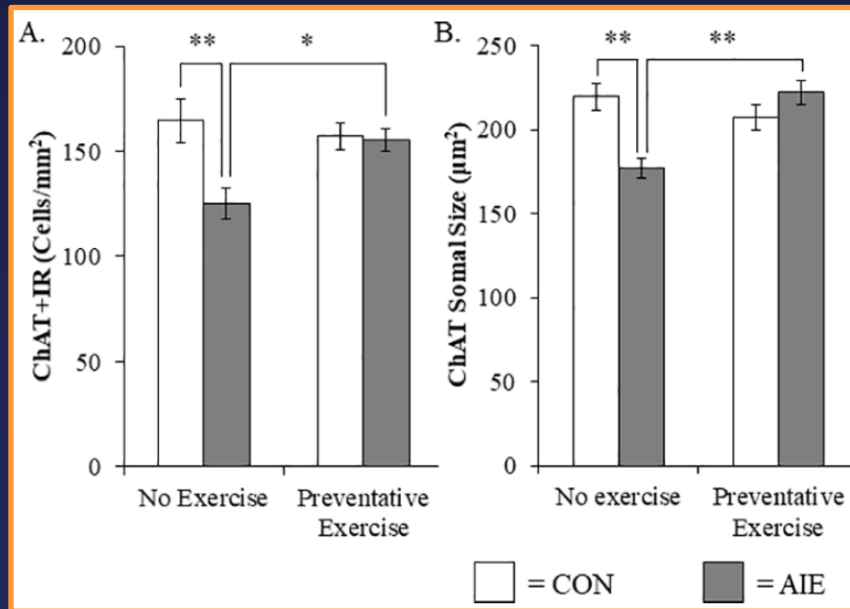
Intestine-restricted delivery of IL-22 reduced ethanol-induced steatohepatitis by increasing expression of Reg3g and preventing bacterial translocation to the liver



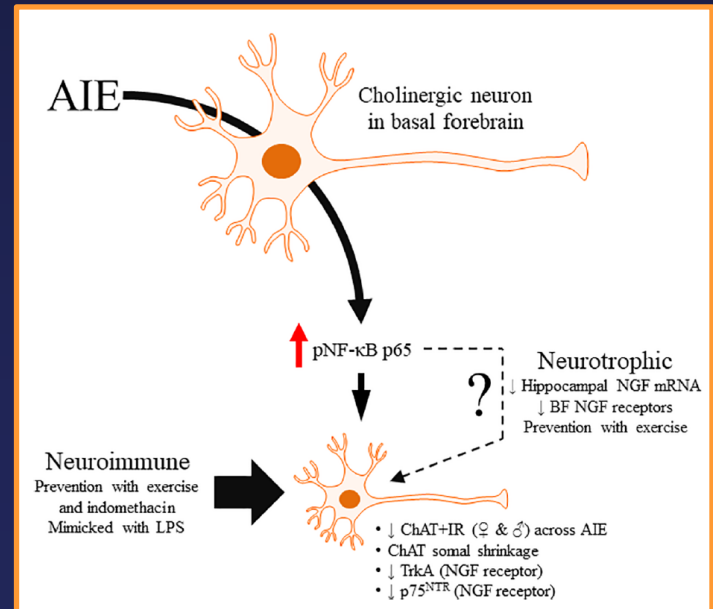
Adolescent Binge Ethanol-Induced Loss of Basal Forebrain Cholinergic Neurons and Neuroimmune Activation are Prevented by Exercise and Indomethacin

This study demonstrates that the loss of basal forebrain cholinergic neurons following adolescent alcohol exposure is accompanied by increased neuroimmune signaling and occurs independently of both sex and timing of adolescent alcohol exposure. In addition to identifying a neuroimmune mechanism for the cell loss, these experiments demonstrated that both exercise and the anti-inflammatory drug indomethacin can prevent alcohol-related cell loss. These findings identify factors that contribute to the adverse effects of adolescent binge drinking on cognitive functioning and suggest preclinical prevention approaches that may be translated to humans.

Exercise prevents cholinergic cell loss in the basal forebrain after adolescent ethanol exposure



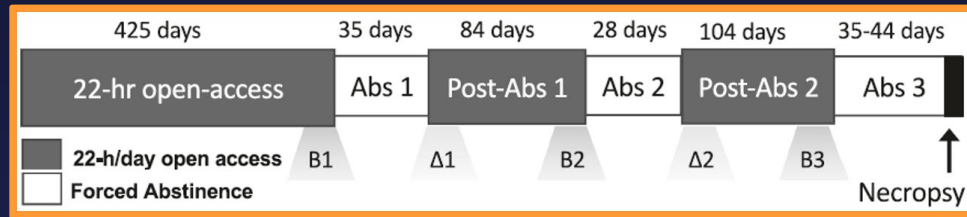
Proposed mechanism underlying the adolescent intermittent ethanol-induced loss of basal forebrain cholinergic neurons



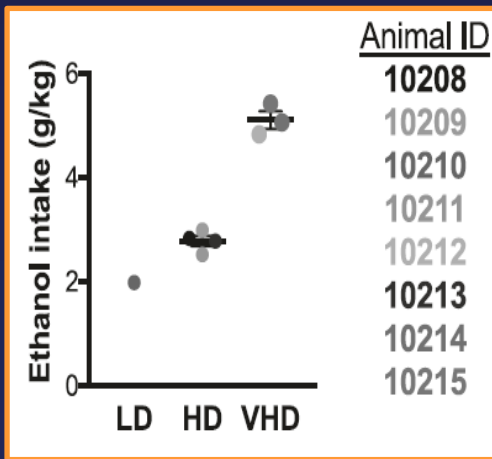
Synaptic Adaptations in the Central Amygdala and Hypothalamic Paraventricular Nucleus Associated with Protracted Ethanol Abstinence in Male Rhesus Monkeys

Aberrant stress regulation contributes to relapse to heavy drinking following prolonged abstinence. This study observed changes in synaptic adaptations in extrahypothalamic (increased GABA release) and hypothalamic (increased glutamate release) stress circuits during abstinence. These findings offer novel insights into the state of brain stress circuitry at a time when relapse is most likely to occur.

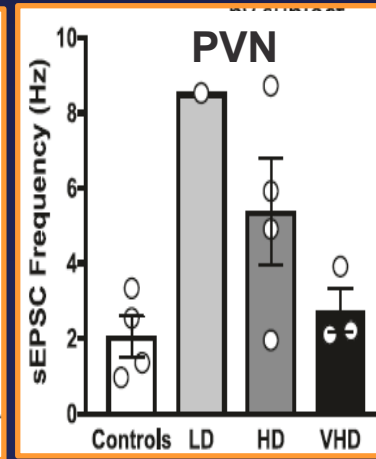
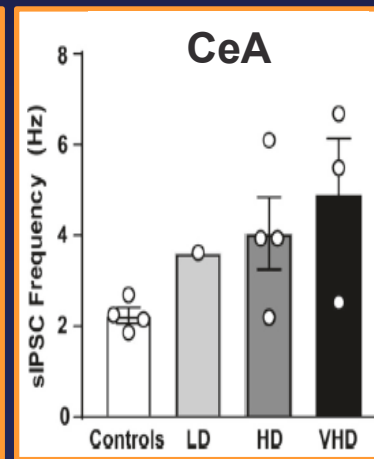
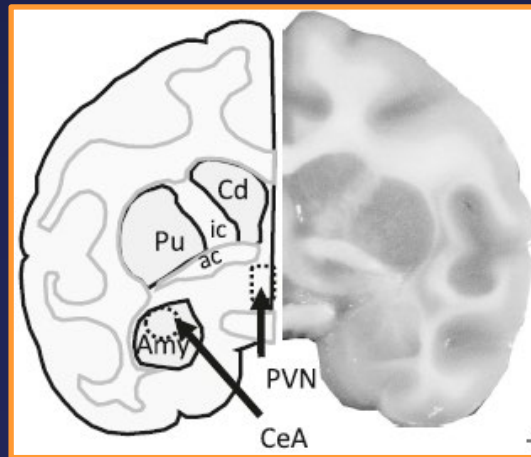
Experimental Timeline



Average daily intake for low, high, and very high drinkers



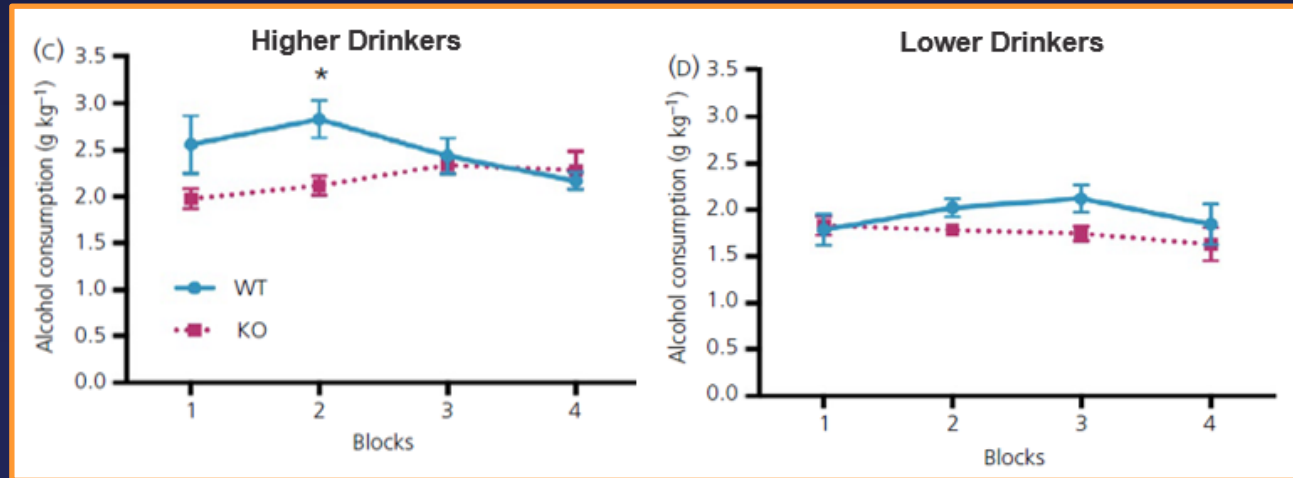
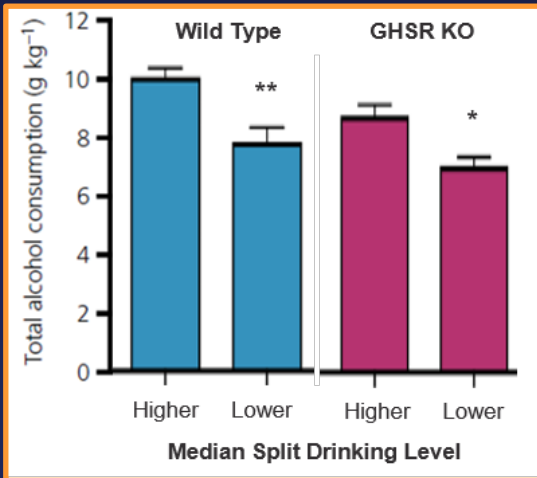
GABA signaling in the CeA and glutamate signaling in the PVN were increased under basal conditions in abstinent drinkers



Ghrelin Receptor Deletion Reduces Binge-Like Alcohol Drinking in Rats

The current study describes the use of a novel transgenic rat model lacking the ghrelin receptor, known as GHSR Knockout (GHSR KO), to examine drinking behavior in multiple experimental paradigms. GHSR KO rats consumed significantly less alcohol in both operant self-administration and binge-like drinking paradigms compared to wild-type rats that express GHSR. These results provide further support for the role of the ghrelin system in AUD and of the potential for GHSR as a novel target in the development of AUD medications.

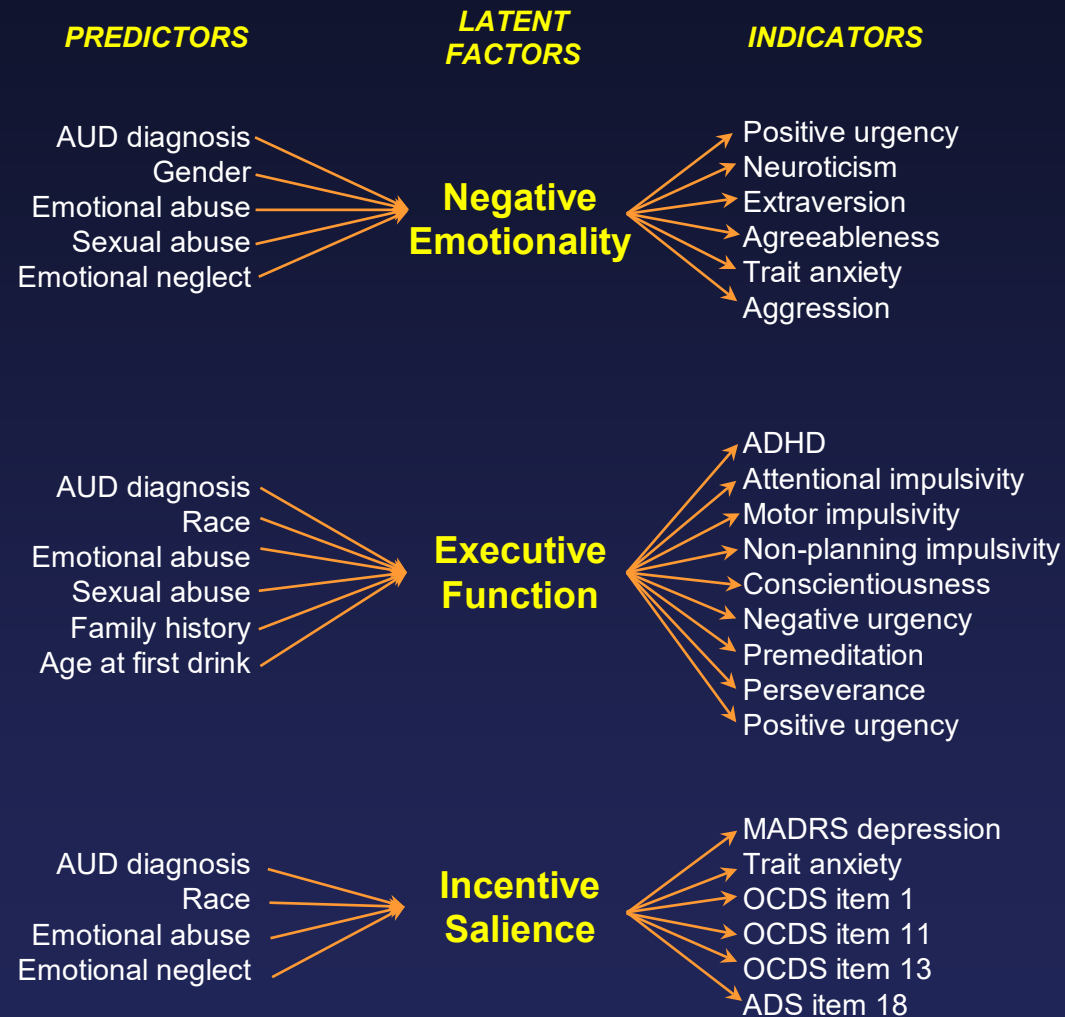
Ghrelin receptor deletion reduced binge-like alcohol intake relative to wild type among higher drinkers



Neurofunctional Domains Derived from Deep Behavioral Phenotyping in Alcohol Use Disorder

This study examined whether three key neurobiological domains that are critical to the addiction cycle (**incentive salience, negative emotionality, and executive function**) could be identified in a large, diverse clinical sample of individuals representing the spectrum of AUD.

Measures of addiction, personality, cognition, behavior, and exposure to early-life stress were collected. Using a multiple indicators, multiple causes approach, the study confirmed the relevance of the three neurofunctional domains to AUD.

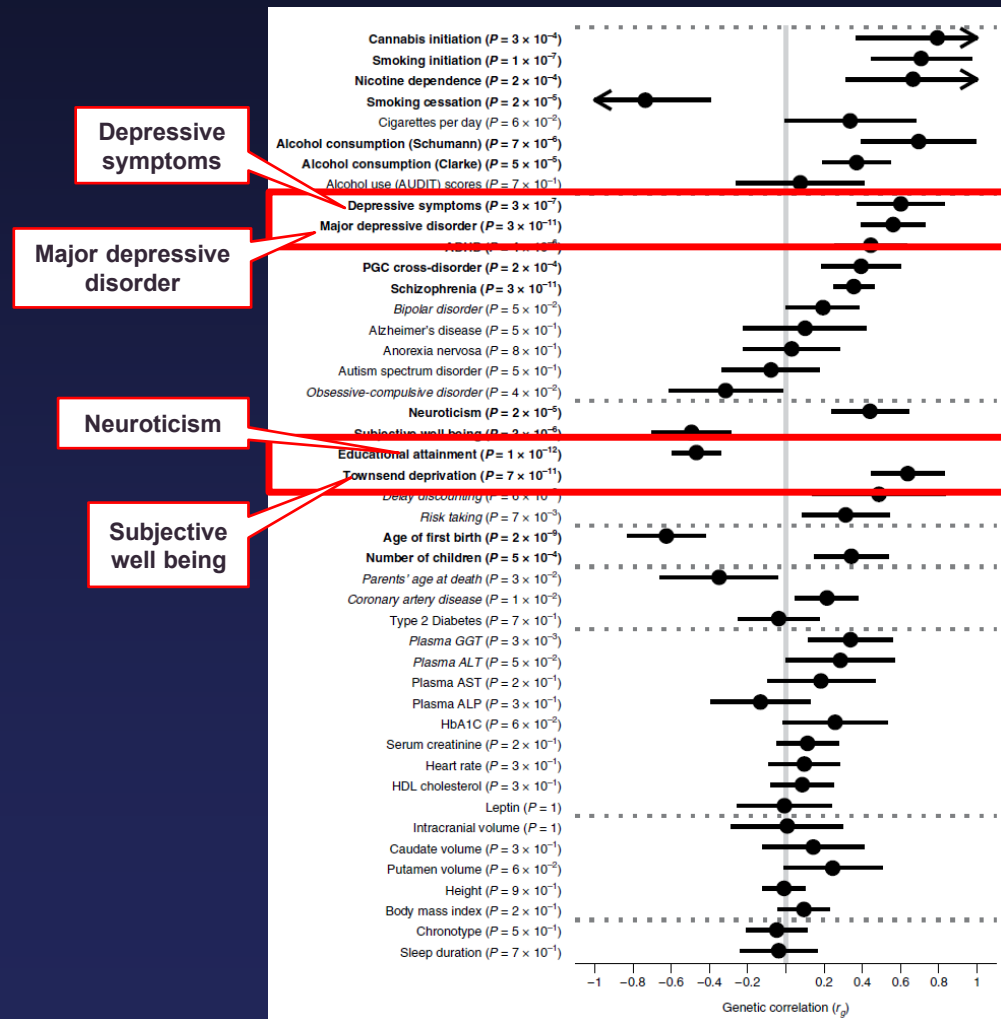


Transancestral GWAS of Alcohol Dependence Reveals Common Genetic Underpinnings with Psychiatric Disorders

In a large genome-wide association study of DSM-IV alcohol dependence (AD), investigators identified variants in the alcohol dehydrogenase (ADH1B) gene as a major contributor to risk for AD in addition to identifying different protective variants in the same gene for individuals of European and African descent.

This analysis also identified robust genetic correlation of AD with a variety of psychiatric outcomes. This correlation was strongest for aspects of negative mood.

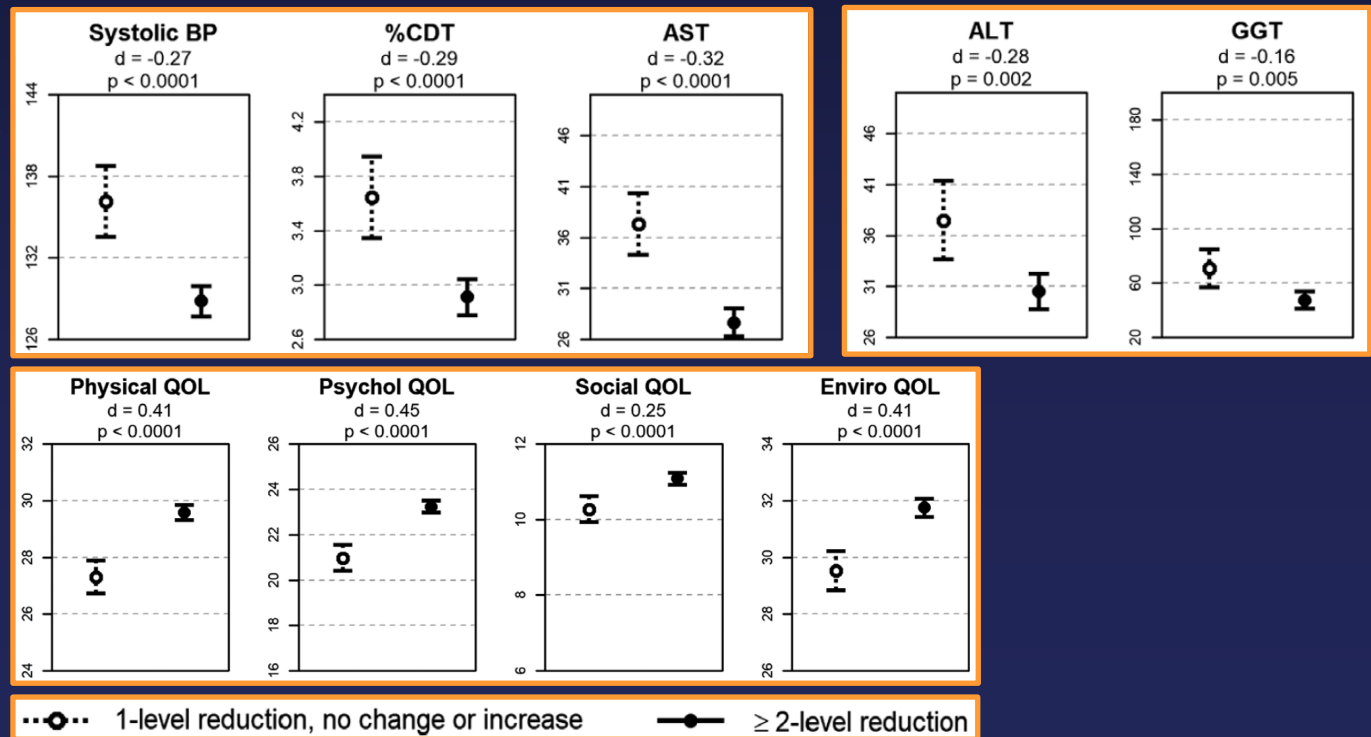
Genetic correlations between traits and alcohol dependence in a European sample



Drinking Risk Level Reductions Associated with Improvements in Physical Health and Quality of Life Among Individuals with Alcohol Use Disorder

To examine the association between the reductions in WHO drinking risk levels and improved alcohol outcomes, a secondary data analysis was conducted using data from patients with AUD. One- and two-level reductions in WHO drinking risk levels were associated with improved physical health and quality of life, supporting the use of this outcome measure as a primary endpoint for AUD clinical trials.

Drinks per day	World Health Organization Alcohol Risk Levels (for males)				World Health Organization Alcohol Risk Levels (for females)			
	Low Risk	Medium Risk	High Risk	Very High Risk	Low Risk	Medium Risk	High Risk	Very High Risk
in grams	1 to 40 g	41 to 60 g	61 to 100 g	101+ g	1 to 20 g	21 to 40 g	41 to 60 g	61+ g
in standard drinks	0 to 2.9 drinks	3.0 to 4.3 drinks	4.4 to 7.1 drinks	7.2+ drinks	0 to 1.4 drinks	1.5 to 2.8 drinks	2.9 to 4.3 drinks	4.4+ drinks



Biomarkers associated with health and liver function

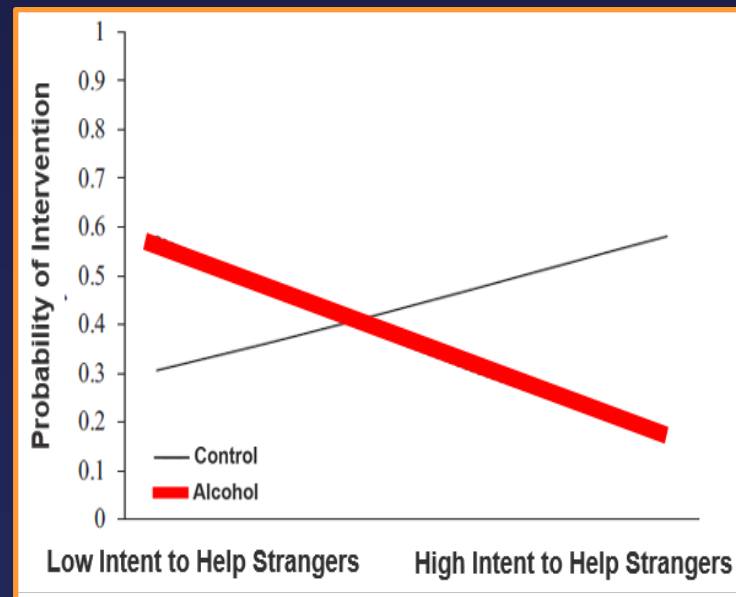
Quality of life measures

Acute Alcohol Intoxication Inhibits Bystander Intervention Behavior for Sexual Aggression Among Men with High Intent to Help

Bystander training programs are a form of primary prevention that aim to reduce sexual aggression, but they rarely focus on training bystanders to intervene effectively when intoxicated. This research evaluated the effects of intent to help strangers and acute alcohol intoxication on the likelihood and speed of sexual aggression intervention.

Results indicated that intent to help strangers is associated with a decreased likelihood of sexual aggression intervention among intoxicated, but not sober, men. Programming efforts should begin accounting for the inhibiting effects of acute alcohol intoxication.

Among men with higher intentions of helping, intoxication decreased the probability of intervening



THANK YOU!

Special thanks to:

Rachel Anderson

Cara Breeden

Vivian Faden

Judit O'Connor

Patricia Powell

Pamela Wernett

Aaron White

Bridget Williams-Simmons