NIAAA Director's Report on Institute Activities to the 153rd Meeting of the National Advisory Council on Alcohol Abuse and Alcoholism

February 6, 2020
Bethesda, MD

50 YEARS
SAVING LIVES THROUGH CUTTING-EDGE RESEARCH
NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

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

NIH National Institute on Alcohol Abuse and Alcoholism

NIAAA Celebrates its 50th Anniversary in 2020

- Special Events will be organized throughout the year, including:
  - Alcohol Research Symposium
    - *NIH Main Campus – March 31*
  - Screening of HBO Documentary "Risky Drinking"
    - *NIH Main Campus – May 19*
  - Special Presentation at RSA/ISBRA
    - *New Orleans, LA – June 21*

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Follow our celebration on social media using #NIAAA50

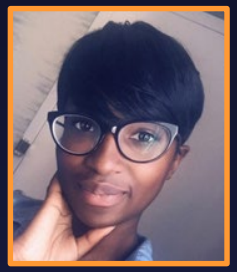
In Memoriam
Richard Veech, M.D., Ph.D.

Dr. Richard Veech, Chief of NIAAA's Intramural Laboratory of Metabolic Control, passed away last week.

He was a world-renowned scientist with expertise in cellular energy metabolism. He is also known for his work that characterized therapeutic benefits of a ketone-rich diet in various metabolic and neurodegenerative disorders.

Dr. Veech served as a scientist in the Federal government for over 50 years.

Welcome to New NIAAA Staff



Emily Brewer joined the Office of the Director as a Program Specialist. She will be supporting OD staff members. Prior to joining NIAAA, she was a Program Analyst at the U. S. Department of Agriculture.

Dr. Luis A. Espinoza joined the Extramural Project Review Branch of the Office of Extramural Activities as the Scientific Review Officer (SRO) of the Clinical, Treatment and Health Services Research Review Subcommittee (AA-3). He previously served as an SRO at the Center for Scientific Review.

Deborah Langer joined the Communications and Public Liaison Branch from the NIH OD Office of Disease Prevention. She will be serving as a communications lead for outreach activities to advance and enhance NIAAA's stakeholder engagement.

Internal staff transitions

Karen Harrington transitioned from her role as the Intramural Section Chief in the Administrative Services Branch to Chief of the Administrative Services Branch.

Departing Staff

Dr. Anita Bechtholt, former Health Science Administrator in the Division of Treatment and Recovery Research, transferred to the National Institute of Mental Health where she now serves as the Associate Director for Research Training & Career Development in the Division of Translational Research.

Bonnie Ellis, Former Administrative Services Branch Chief, accepted a new position as Executive Officer with the NIH Center for Scientific Review.

Dr. Mehdi Farokhnia, Research Fellow in the Laboratory on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, has accepted a position as Staff Scientist at the National Institute on Drug Abuse.

Bridgette Green left her position as a Program Specialist in the Division of Metabolism and Health Effects to join the Nursing Department at the NIH Clinical Center as a Lead Extramural Assistant in September.

Dr. Dale Hereld retired in September after 11 years as a Health Science Administrator in the Division of Metabolism and Health Effects.

Minoo McFarland, Nurse Practitioner with the Laboratory of Neuroimaging, departed NIH to spend time with her family.

Alesia Wilbur, Office of the Director, retired after 30 years of Federal service. During her time at NIAAA, she worked closely with the NIAAA Director and managed administrative staff and functions within the Office of the Director.

FY 2019 NIAAA Budget Closeout

	FY 2019 Enacted Budget
NIH	$39.3 billion
NIAAA	$525.6 million
Research Project Grants	760
Competing Awards	159
Other Research Grants	182
Research Centers	21
Training Positions	326
Research and Development Contracts	$34 million

FY 2020 Budget

- NIH received $41.6 billion ($2.3 B increase from FY19)
  - This funding includes allocations for:
    - Helping to End Addiction Long-term (HEAL) Initiative
    - 21st Century Cures Act
    - BRAIN Initiative
    - Research on influenza
  - Continues support for Gabriella Miller Kids First Act Pediatric Research Initiative
- NIAAA received $545.4 million ($19.8 M increase from FY19)
- FY21 budget is under development.

NIAAA Funding Opportunity Announcements

- **NADIA Consortium: Neurobiology of Adolescent Drinking in Adulthood (U01 Clinical Trial Not Allowed; U24 Clinical Trial Not Allowed)** RFA-AA-20-003; RFA AA 20-004; RFA AA-20-005
- **Impact of Alcohol on the Onset and Progression of Alzheimer's Disease and Its Related Dementias (R01 - Clinical Trial Optional)** RFA-AA-20-006
- **Medications Development for the Treatment of Alcohol Use Disorder (AUD) or Alcohol-Related Organ Damage (AROD), or the Combination of AUD and AROD (U01 Clinical Trial Optional)** RFA-AA-20-007

Notices of Special Interests (NOSI) Issued by NIAAA

- **Administrative Supplements for Regulatory Support for SBIR/STTR Awardees** NOT-AA-19-029
- **Neurobehavioral Mechanisms of Social Isolation and Alcohol Use Disorder** NOT-AA-19-031

NIAAA participation in NIH-wide FOAs

NIAAA is currently participating in over 20 FOAs and NOSIs, including:

- **Identification, Validation, and Manipulation of Neural Circuits Related to Mental Illness and Alcohol and Substance Use Disorders in Non-human Primates (R01) RFA-MH-20-320**
- **Integrative Research on Polysubstance Abuse and Disorder (R61/R33) PAR-20-035**
- **Multiple FOAs in support of career development and diversity in research training:**
  - **BRAIN Initiative Advanced Postdoctoral Career Transition Award to Promote Diversity (K99/R00)**
  - **Maximizing Opportunities for Scientific and Academic Independent Careers (MOSAIC) Postdoctoral Career Transition Award to Promote Diversity (K99/R00)**
  - **Administrative Supplements to Promote Research Continuity and Retention of NIH Mentored Career Development Award Recipients and Scholars (K)**
  - **NIH Blueprint Program for Enhancing Neuroscience Diversity through Undergraduate Research Education Experiences (R25)**
- **Multiple FOAs related to Sex and Gender influences**
- **For full listing, please refer to the Director's Report.**

NIAAA Research in the News

- Analysis of death certificate data revealed that alcohol-related mortality **doubled** from 1999 to 2017
  - Death rates were highest among men and middle-aged and older adults (ages 45-74)
  - Death rates increased over time across all age groups except 16-20 and 75+
  - Increase in death rate over time was greater in women than men
- These statistics align with other recent reports that have highlighted changing trends in drinking patterns and increased consequences of alcohol in **women** and the **aging population**
- Mortality data linked alcohol use to "deaths of despair" (suicide, drug overdose, liver disease)

Citation: White AM, Castle IP, Hingson RW, and Powell PA. *Alcohol Clin Exp Res*. 44(1):178-187.

Coming up: National Drugs and Alcohol Chat Day

- National Drugs and Alcohol Chat Day is an annual live online chat held between high school students and NIH scientists during *National Drug and Alcohol Facts Week*®.
- Students from around the country ask the questions they most want the answers to about drugs and drug misuse, including drug effects, how to help friends or family that are using drugs, and what causes addiction. Expert scientists give them the facts.

Chat Day will be held on April 1, 2020.

Registration opens February 24.

Are we experiencing a cultural shift in attitudes about alcohol use?

- Observance of sober months (Dry January, Sober October, etc) is gaining popularity
- Sober Curious movement is also receiving a lot of attention: Practicing mindfulness versus going along with the dominant drinking culture
- These trends, largely driven by millennials, encourage a focus on wellness

U.S. Dietary Guidelines for Alcohol Consumption

- **For adults 21 and older:**
  - No more than 2 drinks per day for men
  - No more than 1 drink per day for women
- **For individuals under age 21:**
  - No alcohol*
- **Others should avoid alcohol completely, including those who:**
  - Plan to drive or operate machinery, or participate in activities that require skill, coordination, and alertness
  - Have certain medical conditions or take certain medications
  - Are recovering from alcohol use disorder or are unable to control the amount that they drink
  - Are pregnant or trying to become pregnant

**The National Minimum Legal Drinking Age Act requires that States prohibit persons under 21 years of age from purchasing or publicly possessing alcoholic beverages as a condition of receiving State highway funds.*

Research Highlights

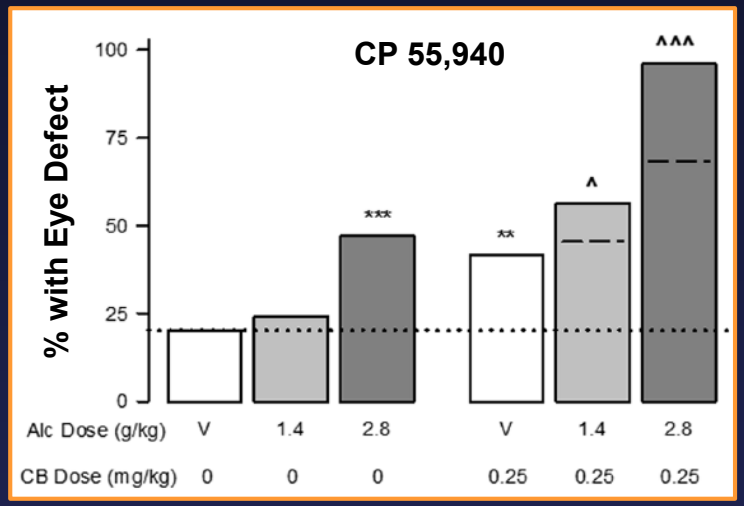
Cannabinoids Exacerbate Alcohol Teratogenesis by a CB1-Hedgehog Interaction

Using animal models of prenatal substance exposure, this study demonstrated that a single exposure to cannabinoids (CB) caused craniofacial and brain malformations similar to those caused by prenatal alcohol exposure.

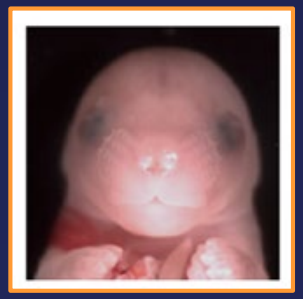
Mechanistic studies in this report indicated that both alcohol and CB converge to inhibit the Sonic Hedgehog (Shh) pathway, an important molecular signal for normal development.

These findings shed light on the mechanism of alcohol and CB-induced birth defects and further highlight the dangers of co-substance use during pregnancy.

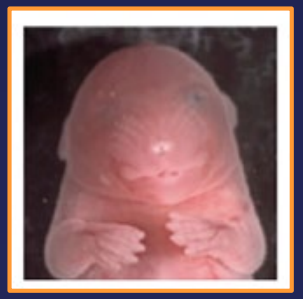
Cannabinoids exacerbate alcohol-induced eye and face malformations



Typical fetal mouse face



Craniofacial malformations following exposure to alcohol and CB



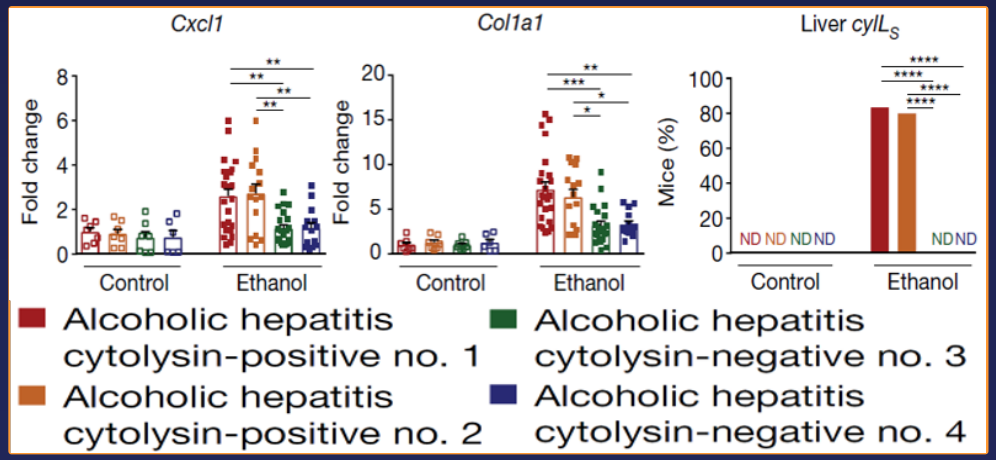
Citation: Fish EW, Murdaugh LB, Zhang C, Boschen KE, Boa-Amponsem O, Mendoza-Romero HN, Tarpley M, Chdid L, Mukhopadhyay S, Cole G, Williams KP, and Parnell SE. *Sci Rep.* 2019 Nov 5;9(1):16057.

Bacteriophage Targeting of Gut Bacterium Attenuates Alcoholic Liver Disease

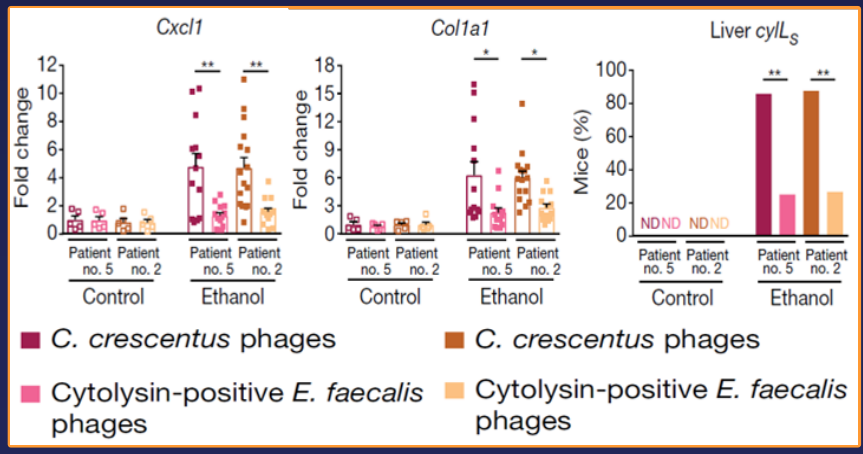
This report demonstrates that the presence of cytolysin-positive *E. faecalis*, a bacterium that secretes the cell-destroying toxin cytolysin, in the gut correlates with severity of liver disease and mortality in patients with alcoholic hepatitis.

Further, using a mouse model of alcohol-associated liver disease, the study also demonstrated that bacteriophages that specifically target cytolysin-positive *E. faecalis* are effective in reducing liver injury, suggesting a potential therapeutic target for the treatment of alcoholic hepatitis.

Fecal transplant from cytolysin-positive patients with alcoholic hepatitis increases markers of alcohol-induced liver inflammation, fibrosis, and cytolysin-associated damage in mice.



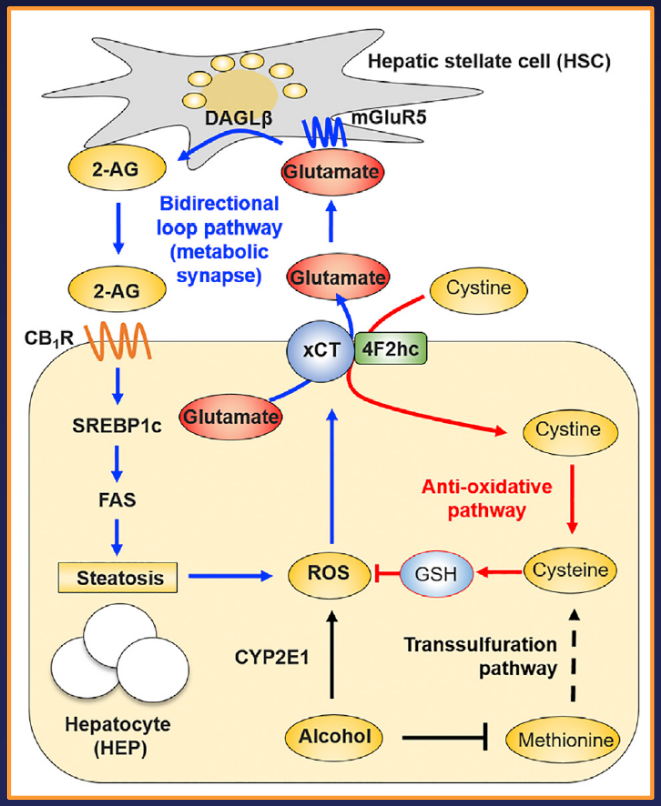
Phage therapy against cytolytic E. faecalis reverses alcohol-induced liver damage.



Citation: Duan Y, Llorente C…Fouts DE, and Schnabl B. *Nature*. 2019 Nov;575(7783):505-511.

Glutamate Signaling in Hepatic Stellate Cells Drives Alcoholic Steatosis

Previous research has shown that increased glutamate signaling in the brain plays a role in driving alcohol-seeking behavior through actions at the metabotropic glutamate receptor. The current study demonstrates that glutamate signaling via these receptors is also involved in mediating alcohol-associated fatty liver disease.



- ***Alcohol consumption increases xCT (cystine-glutamate anti-porter) expression in hepatocytes***
- ***xCT-derived glutamate release increases expression of mGluR5 in hepatic stellate cells***
- ***mGluR5 stimulates 2-AG production in hepatic stellate cells to influence lipogenesis of hepatocytes via CB1R***
- ***Inhibition of xCT and mGluR5 blocks alcoholic steatosis in liver***

These results suggest that inhibition of a single pharmacological target, mGluRs, may have therapeutic value in the treatment of both alcohol use disorder and alcohol-induced liver damage.

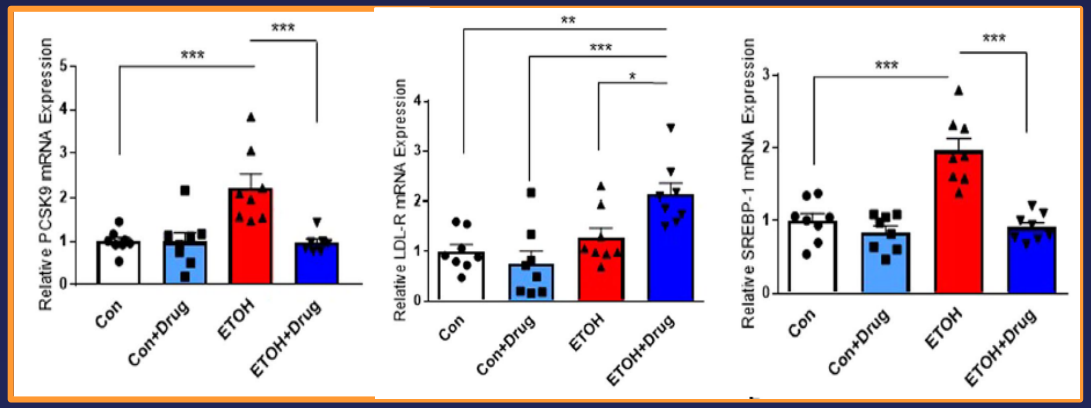
Citation: Choi WM, Kim HH, Kim MH, Cinar R, Yi HS, Eun HS, Kim SH, Choi YJ, Lee YS, Kim SY, Seo W, Lee JH, Shim YR, Kim YE, Yang K, Ryu T, Hwang JH, Lee CH, Choi HS, Gao B, Kim W, Kim SK, Kunos G, and Jeong WI. *Cell Metab*, 30 (5), 877-889.e7

PCSK9 Inhibition as a Novel Therapeutic Target for Alcoholic Liver Disease

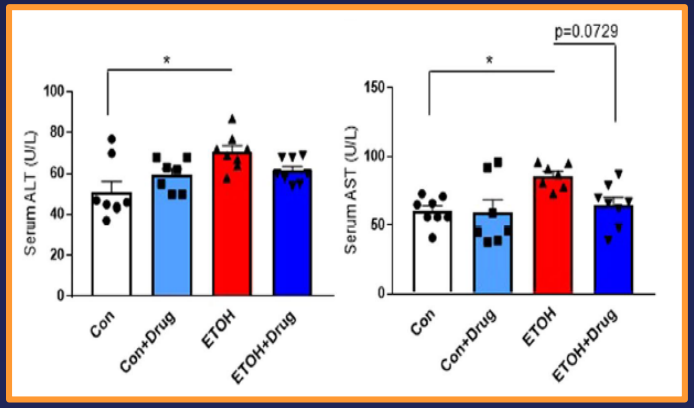
Proprotein convertase subtilisin/kexin 9 (PCSK9) has been identified as a plausible new target for AUD and alcohol-associated liver disease (ALD). This study tested the PCSK9 inhibitor alirocumab, a monoclonal antibody that robustly reduces low-density lipoprotein (LDL) cholesterol, in a rat model of chronic alcohol exposure.

The findings demonstrated that alirocumab significantly reduced alcohol-induced hepatic triglyceride accumulation, hepatocellular injury, and hepatic inflammation. Further research is needed to investigate the therapeutic efficacy and safety of anti-PCSK9 treatment in individuals with AUD and ALD.

Alirocumab treatment attenuated alcohol-induced PCSK9 mRNA elevation and upregulated LDL-receptor via modulation of transcription factors including SREBP-1



Alirocumab attenuated alcohol-induced expression of biomarkers for liver injury: ALT and AST



Citation: Lee JS, Mukhopadhyay P, Matyas C, Trojnar E, Paloczi J, Yang YR, Blank BA, Savage C, Sorokin AV, Mehta NN, Vendruscolo JCM, Koob GF, Vendruscolo LF, Pacher P, and Lohoff FW. *Sci Rep*, 9 (1), 17167. 2019 Nov 20

Early Detection and Staging of Chronic Liver Diseases with a Protein MRI Contrast Agent

This study reports the development of a sensitive protein-based magnetic resonance imaging (MRI) contrast agent, ProCA32.collagen1, that can detect and accurately quantify early stage fibrosis in mouse models of alcohol-, diet- and chemical-induced liver diseases.

With further validation, this contrast agent could potentially be used to noninvasively and accurately detect early stage fibrosis in liver and other organs, allowing for earlier treatment and better patient outcomes.

ProCA32.collagen1 enhanced MRI can demonstrate different collagen distribution in 3 different models of liver fibrosis

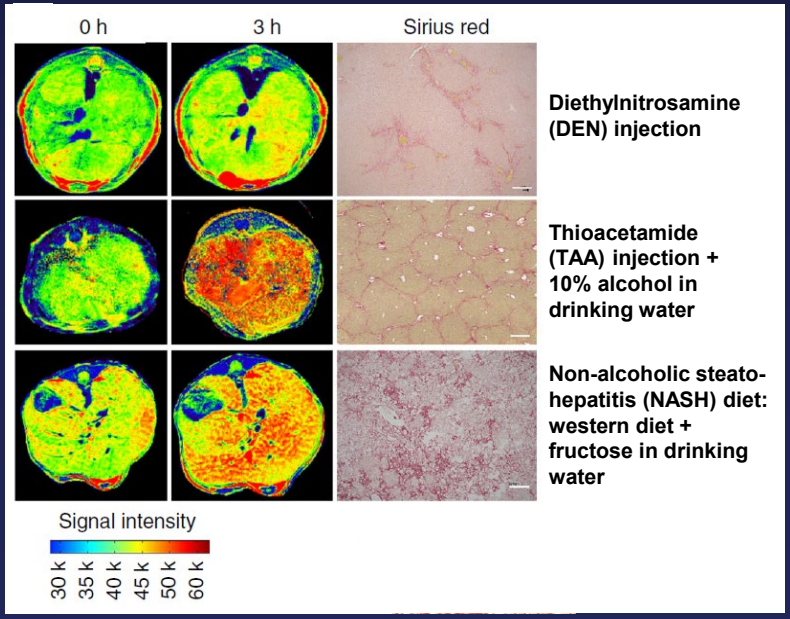
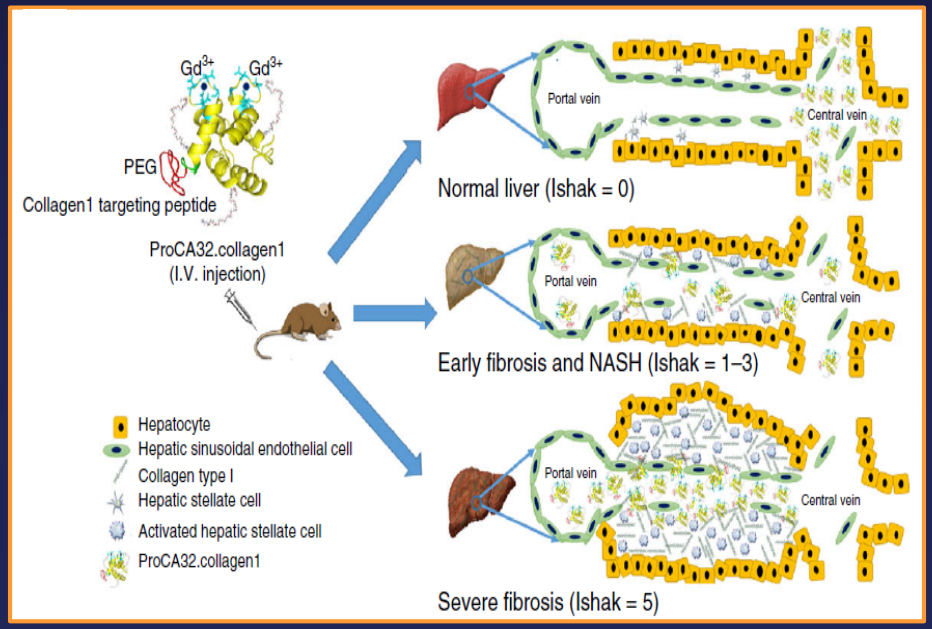


Illustration of ProCA32.collagen1 distribution and suggested mechanism in different stages of fibrosis



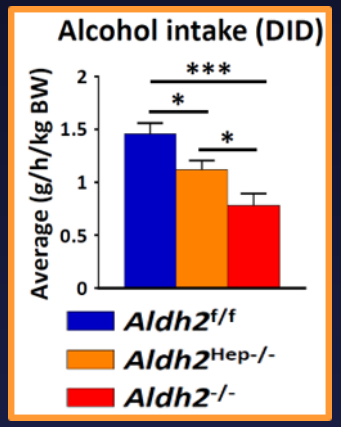
Citation: Salarian M, Turaga RC, Xue S, Nezafati M, Hekmatyar K, Qiao J, Zhang Y, Tan S, Ibhagui OY, Hai Y, Li J, Mukkavilli R, Sharma M, Mittal P, Min X, Keilholz S, Yu L, Qin G, Farris AB, Liu ZR, and Yang JJ. *Nat Commun.* 2019 Oct 29;10(1):4777

Targeting Liver Aldehyde Dehydrogenase-2 Prevents Heavy but Not Moderate Alcohol Drinking

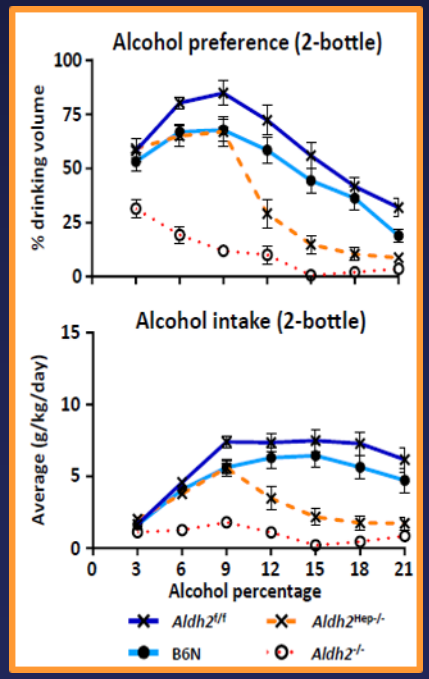
Systemic ALDH2 inhibition by disulfiram has side effects that pose clinical limitations. Using mice with liver-specific *Aldh2* gene deletion (compared to global knockout), researchers found that although the liver only contributes to ~half of acetaldehyde clearance, knockdown of *Aldh2* in the liver still reduced alcohol intake.

These results suggest that liver-specific ALDH2 inhibition may be a potential treatment approach for AUD.

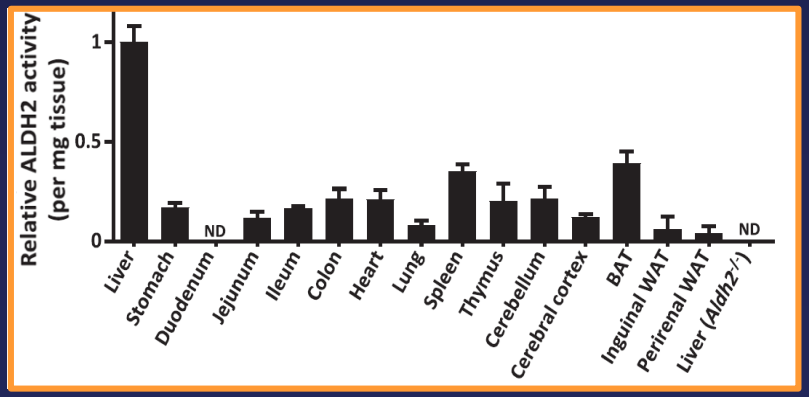
Genetic deletion of liver-specific Aldh2 decreased alcohol intake in a binge-like drinking model, but not as robustly as global deletion



Genetic deletion of liver-specific Aldh2 decreased preference and intake of alcohol at high concentrations ("heavy drinking") but not low concentrations ("moderate drinking")



Cumulative effects of ALDH2 produced by other organs may also contribute to acetaldehyde metabolism



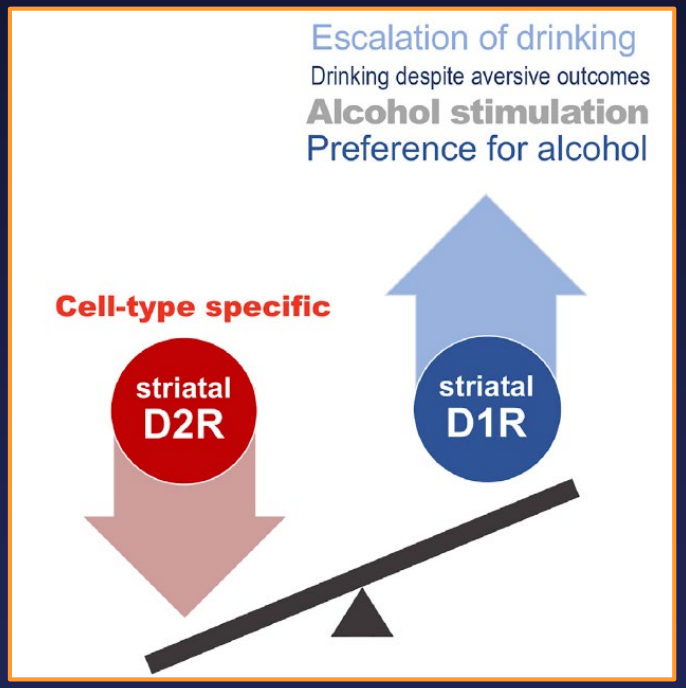
Citation: Guillot A, Ren T, Jourdan T, Pawlosky RJ, Han E, Kim SJ, Zhang L, Koob GF, and Gao B. *Proc Natl Acad Sci U S A*. 2019 Dec 2. pii: 201908137.

A Mechanism Linking Two Known Vulnerability Factors for Alcohol Abuse: Heightened Alcohol Stimulation and Low Striatal Dopamine D2 Receptors

Heightened sensitivity to alcohol's stimulating effects has predictive value for alcohol misuse.

Using transgenic mice and other genetic manipulations, this study provided direct evidence that lowering levels of D2 receptors on striatal projection neurons heightens alcohol-related stimulatory effects and escalation of alcohol intake, which continues despite aversive outcomes.

The study also demonstrated that upregulation of dopamine D1 receptor functioning is responsible for these effects, suggesting that **low striatal D2 receptor levels trigger D1 receptor hypersensitivity, ultimately leading to compulsive-like drinking and other factors related to risk for alcohol use disorder.**



Citation: Bocarsly MR, da Silva e Silva D, Kolb V, Luderman KD, Shashikiran S, Rubinstein M, Sibley DR, Dobbs LK, and Alvarez VA. *Cell Rep*, 29 (5), 1147-1163.e5.

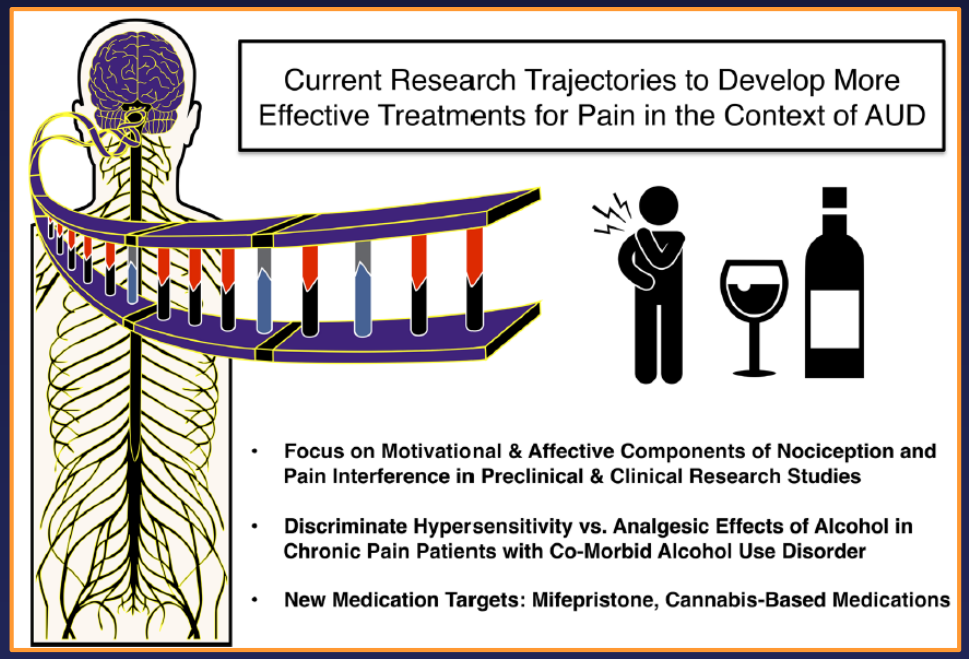
Alcohol and Pain: A Translational Review of Preclinical and Clinical Findings to Inform Future Treatment Strategies

Alcohol use disorder (AUD) and chronic pain are pervasive conditions with a high rate of comorbidity.

This review establishes a broader translational focus on persistent pain and alcohol use that

- provides updates on recent models and research
- describes overlapping behavioral, social, and biological mechanisms
- assesses evidence for informing treatment recommendations and future research that intersect pain and AUD

Recommended research trajectories for the treatment of pain and AUD

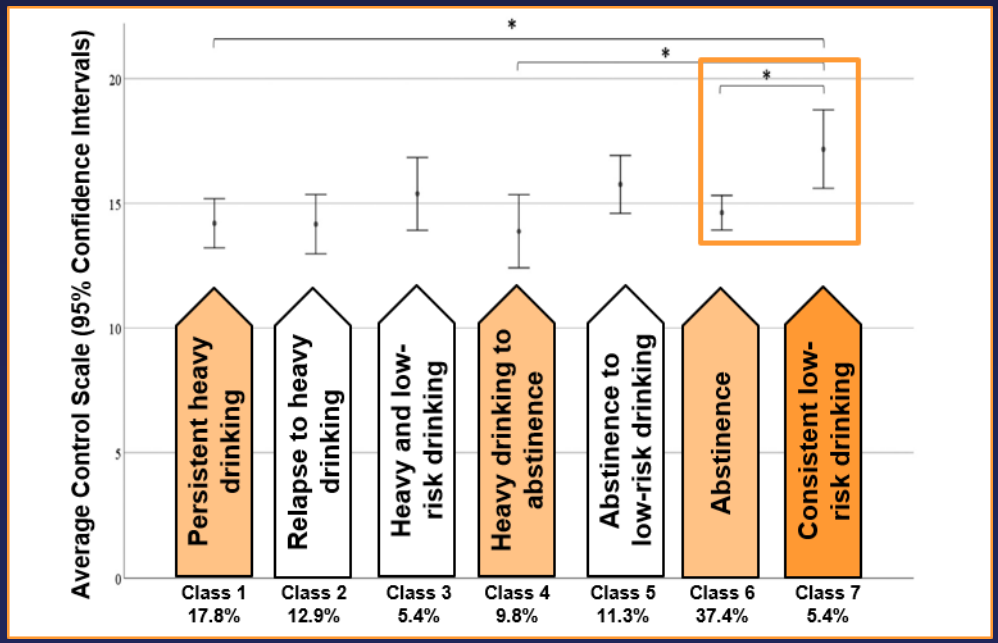


Citation: Edwards S, Vendruscolo LF, Gilpin NW, Wojnar M, Witkiewitz K. *Alcohol Clin Exp Res.* 2019 Dec 16

Trait Self-Control Predicts Drinking Patterns During Treatment for Alcohol Use Disorder and Recovery Up to Three Years Following Treatment

Previous research has identified demographic and clinical indicators related to recovery outcomes, but behavioral traits such as self-control have received less attention. Using latent class analysis, this study confirmed seven classes of drinking patterns among participants in treatment identified in previous research and compared baseline self-control across classes.

The consistent low-risk drinking group had significantly higher self-control than both persistent heavy drinking and consistent abstinence groups.



This finding has important clinical implications, suggesting that achieving low-risk drinking throughout treatment may require even more self-control than achieving abstinence.

Low-risk drinking was defined in this study as one or more days of drinking in a given week, but no "heavy drinking days" (4+/5+ drinks in a day for women/men).

Citation: Stein E and Witkiewitz K. *Addict Behav*, 99, 106083. Dec 2019

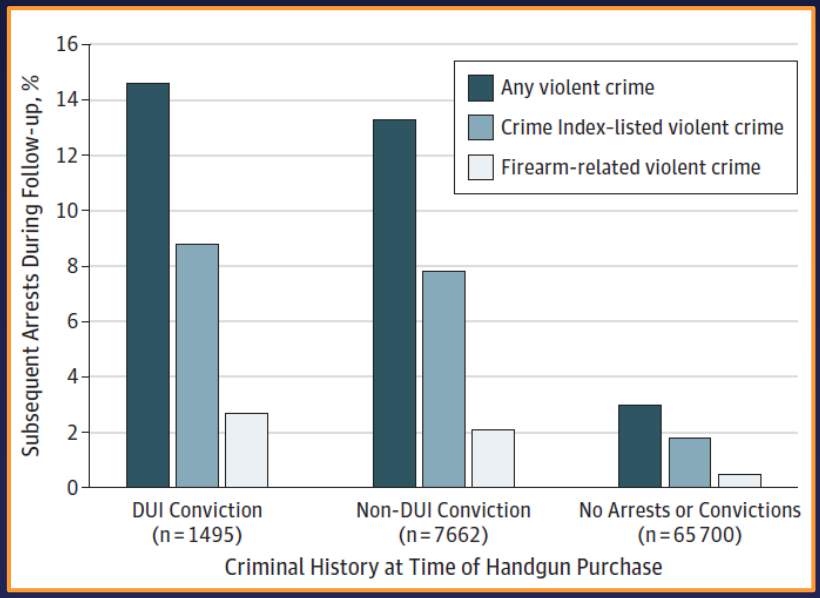
Association of Prior Convictions for Driving Under the Influence with Risk of Subsequent Arrest for Violent Crimes Among Handgun Purchasers

In this study of authorized handgun purchasers in California, history of DUI conviction at the time of purchase was associated with a significant increase in the risk of subsequent arrest for a violent crime, independent of a range of individual and community-level measures.

Purchasers with a previous DUI conviction and other non-DUI arrests or convictions were at greatest risk of subsequent arrest for a violent crime.

This finding extends previous links between alcohol use and violence specifically to legal purchasers of handguns, suggesting that alcohol-related prohibitions on firearms purchase based on DUI convictions may reduce firearm-related injury and death.

Subsequent arrests for violent crimes are higher among individuals with a DUI or non-DUI conviction prior to legal handgun purchase



Citation: Kagawa RMC, Stewart S, Wright MA, Shev AB, Pear VA, McCort CD, Pallin R, Asif-Sattar R, Sohl S, Kass PH, Cerdá M, Gruenewald P, Studdert DM, and Wintemute GJ. *JAMA Intern Med.* 2019 Sep 30.

THANK YOU!

Special thanks to:

Rachel Anderson

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Patricia Powell

Pamela Wernett

Aaron White

Bridget Williams-Simmons

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