

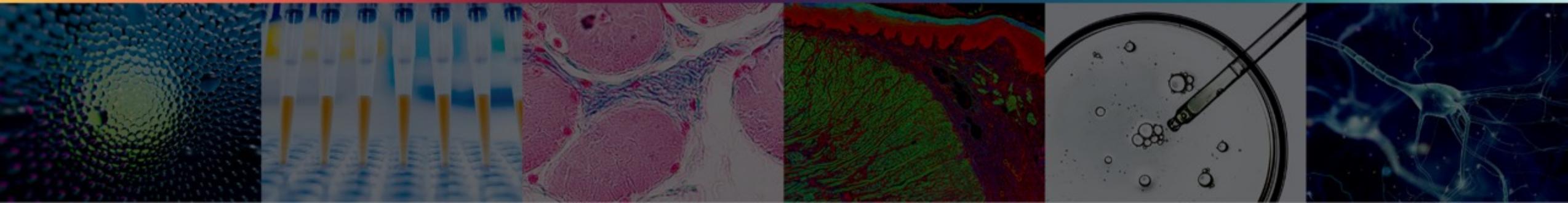


Frontiers in alcohol addiction science and medicine

Marisa Roberto, PhD
Schimmel Family Chair

Professor and Vice Chair, Department of Molecular Medicine
Professor, Department of Neuroscience

Wednesday, August 10, 2022 | 1:00 pm PT/4:00 pm ET





The Roberto lab seeks to understand the neuronal mechanisms that underlie synaptic and/or molecular changes to influence the development of dependence to alcohol and other drugs of abuse.

Marisa Roberto, PhD

Schimmel Family Chair

Professor and Vice Chair, Department of Molecular Medicine

Professor, Department of Neuroscience



THE
FRONT
ROW
at Scripps Research

PECASE Award

Roberto is a recipient of the U.S. Presidential Early Career Award for Scientists and Engineers (PECASE), **the highest honor bestowed by the U.S. government** on outstanding scientists and engineers beginning their independent careers. She received the award in 2009.



THE
FRONT
ROW

at Scripps Research

Did you know??

Roberto has been knighted by Italy, her country of birth. In 2011, she was awarded the Cavaliere (knight) degree, a rank within the Order of Merit of the Italian Republic—the country’s highest honor—in recognition of her scientific research in the neurobiology of addictive behavior.

She can be addressed as *Cavaliere Roberto*.



THE
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ROW

at Scripps Research

An international influence.

Roberto has organized four editions of the International Congress on Alcoholism and Stress, helping the event in 2008, 2011, 2014 and 2017. The international meeting aims to bridge ongoing independent programs on stress and alcoholism mechanisms in Europe and the U.S.



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at Scripps Research



Frontiers in Alcohol Addiction Science and Medicine

Marisa Roberto, Ph.D

The Scripps Research Institute

August 10th, 2022

The Department of Molecular Medicine

Schimmel Family Chair

The Pearson Center for Alcoholism and Addiction Research

The Scripps Research Institute and Alcohol Research Center

Outline

- Introduction: Addiction and Alcohol Use Disorder (AUD)

Brain Disorder: **Amygdala**

- Recruitment of Stress Systems
- Recruitment of Neuroimmune Systems



What is Addiction?

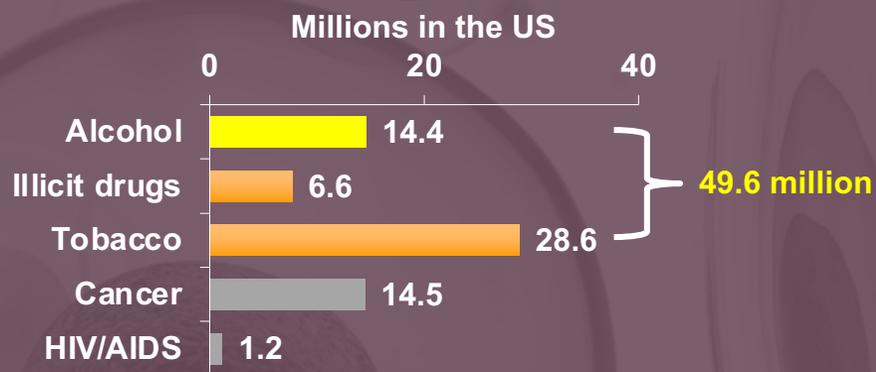
In Numbers- Why it Matters





Addiction is Very Common and Costly

Prevalence of disorder/disease



Cost to society



NIH Budget





- Alcohol misuse is often comorbid with other mental illnesses (e.g., depression, anxiety, etc.)
- Commonly used to cope with symptoms (self-medication)
- Similarly, mental health conditions complicate treatment for AUD

The Elephant in the Room



The “stigma” limits individuals who suffer from addiction to seek treatment.

*Volkow, Gordon, Koob,
Neuropsychopharmacology, 2021*

“I’m right here in the room and no one even acknowledges me.”

CartoonStock.com

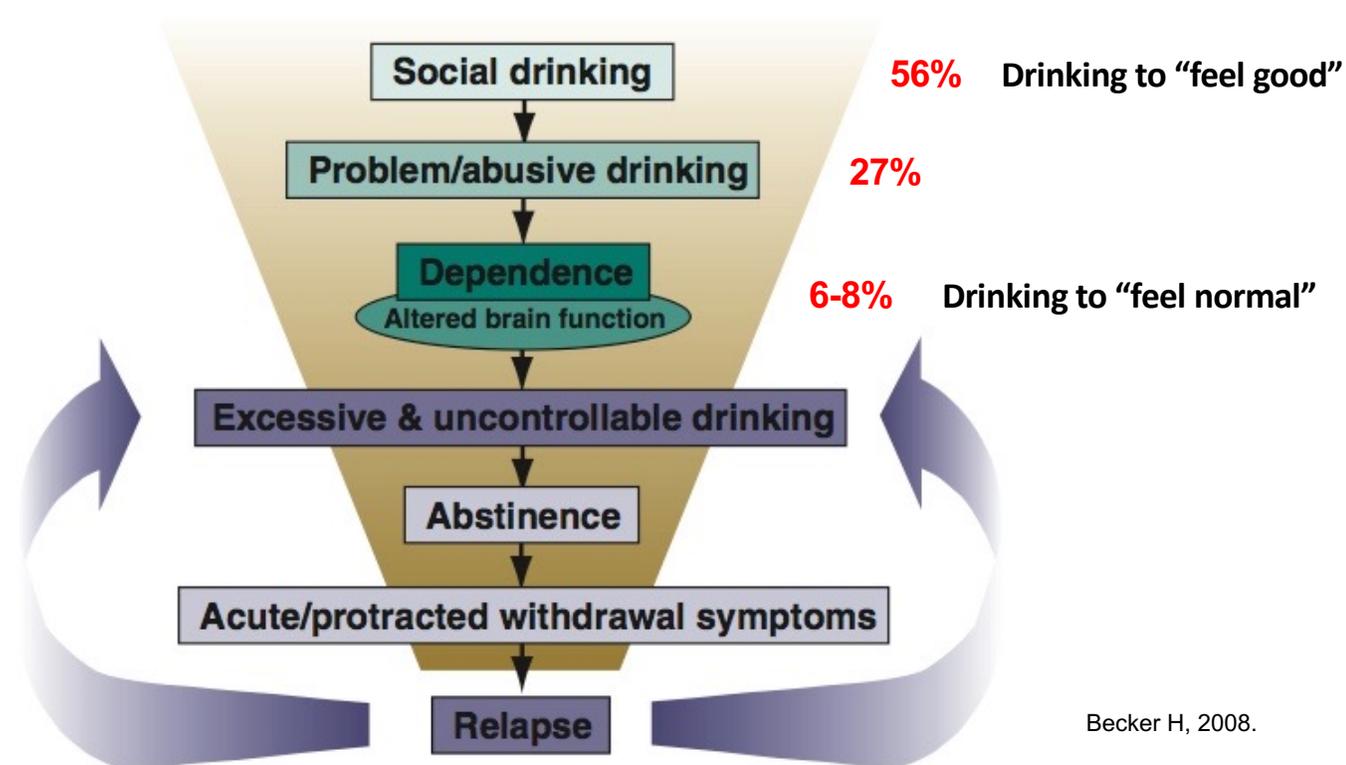
New Yorker cartoon

Factors Associated with Increased Drinking During the Pandemic

A recent systematic review reported that an increase in drinking during the pandemic is associated with:

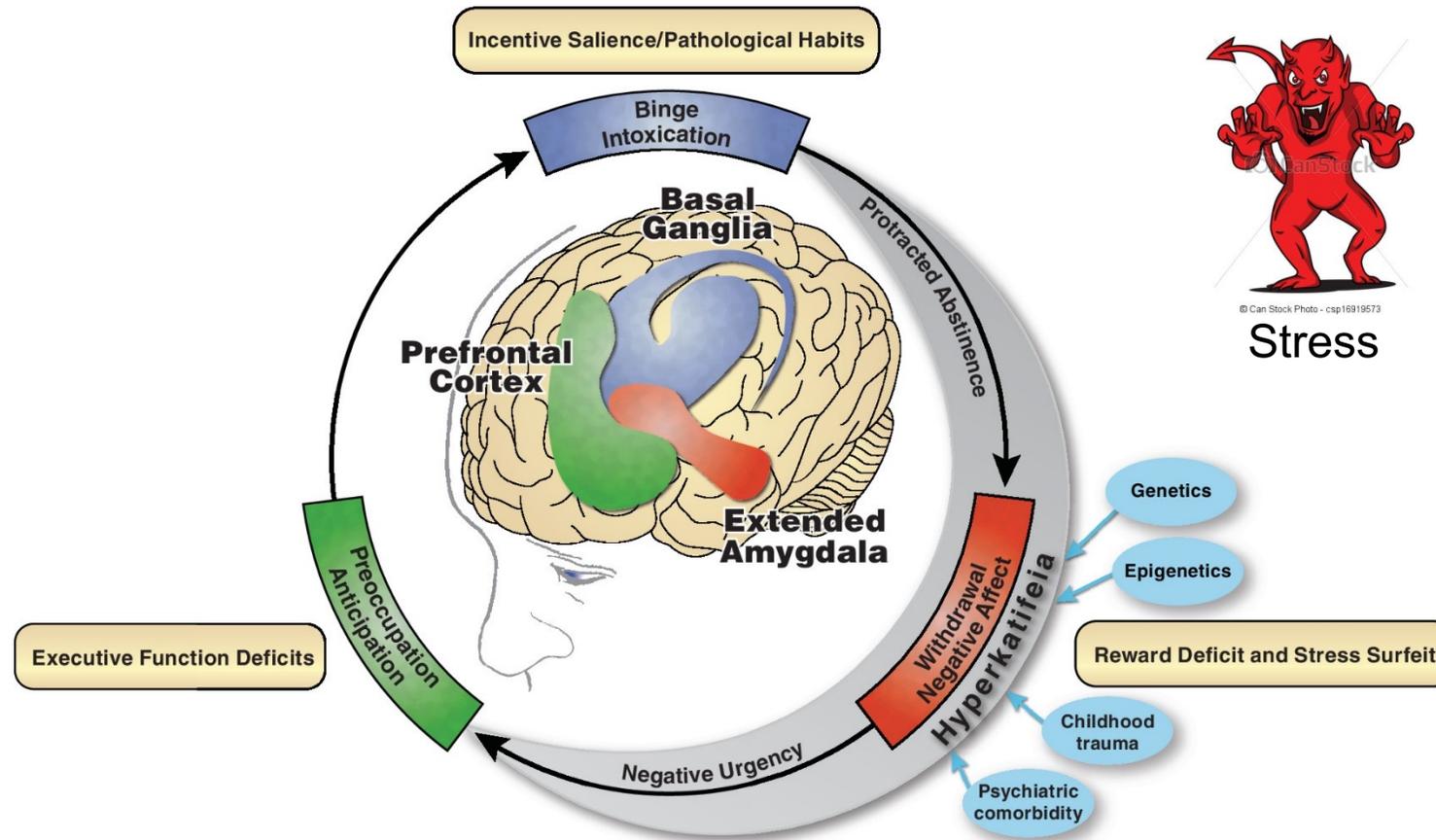
- Social Isolation
- Income loss/financial stress
- Greater depression or anxiety, and general psychological distress
- **Greater drinking to cope with stress**

Stages of Alcohol Use Disorder (AUD)



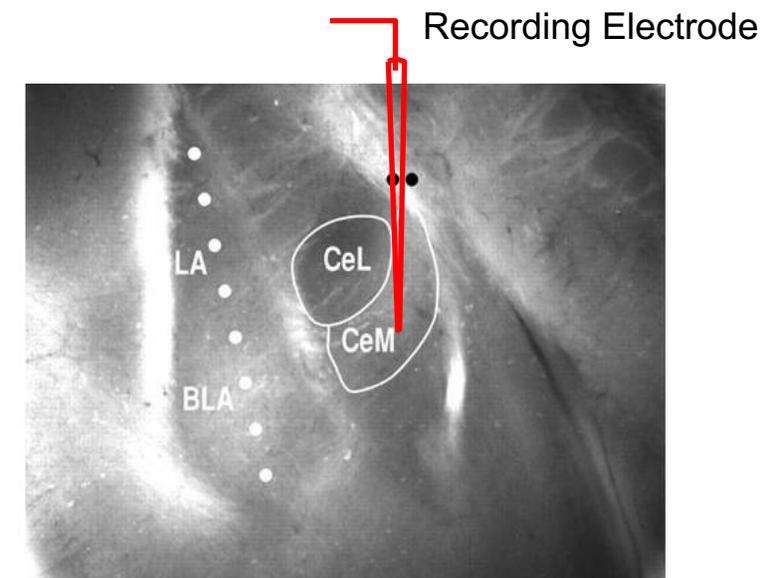
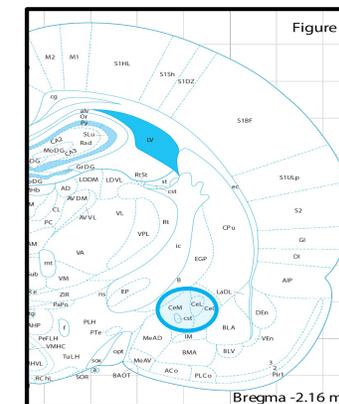
AUD is a chronically relapsing disorder that is progressive and has serious detrimental health outcomes as defined by: **1)** compulsion to seek and take alcohol, **2)** loss of control in limiting alcohol intake, and **3)** emergence of a negative emotional state (e.g., anxiety, etc.) when access to the drug is prevented

Conceptual Framework for Neurobiology of AUD

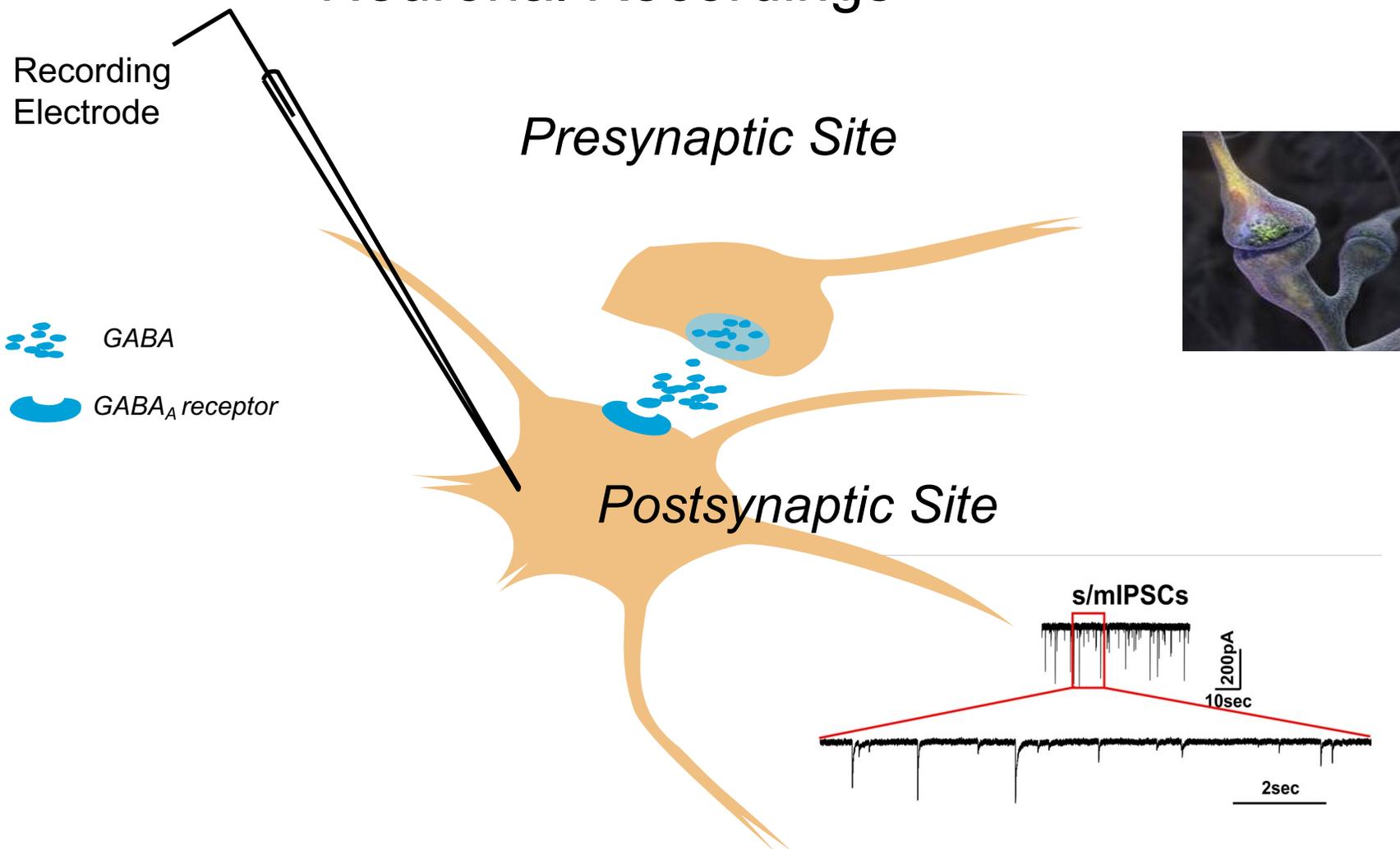


Central Nucleus of Amygdala (CeA)

- Implicated in behaviors related to fear, stress, anxiety.
- Predominantly inhibitory GABAergic neurons containing numerous neuropeptides including stress-related peptides.
- GABAergic transmission plays an important role in mediating **alcohol- and stress-related behaviors**.



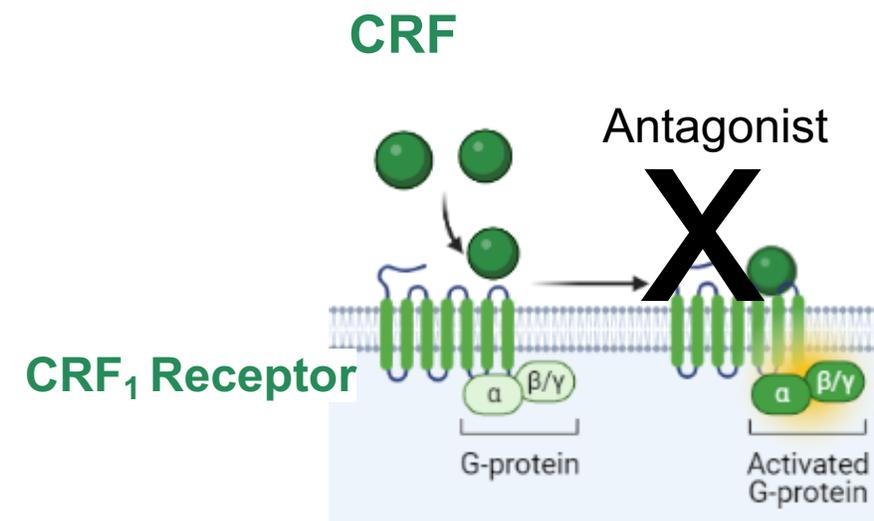
Neuronal Recordings



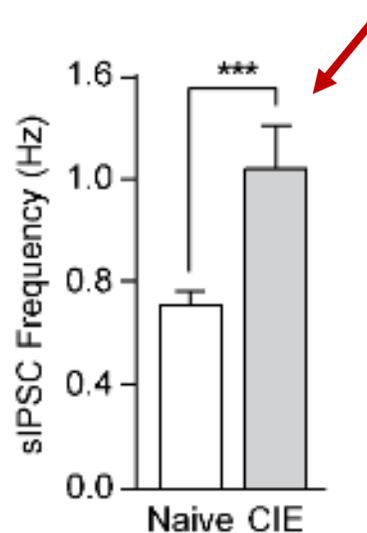
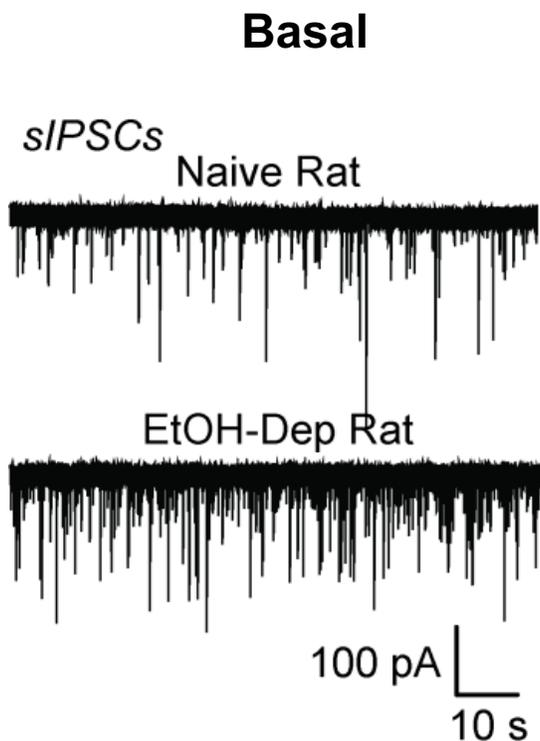
Whole-cell voltage-clamp recordings of spontaneous and miniature GABA_A inhibitory post-synaptic currents [sIPSCs and mIPSCs (in TTX)] in glutamate and GABA_B receptor blockers

Corticotropin Releasing Factor (CRF) Regulates Stress Responses

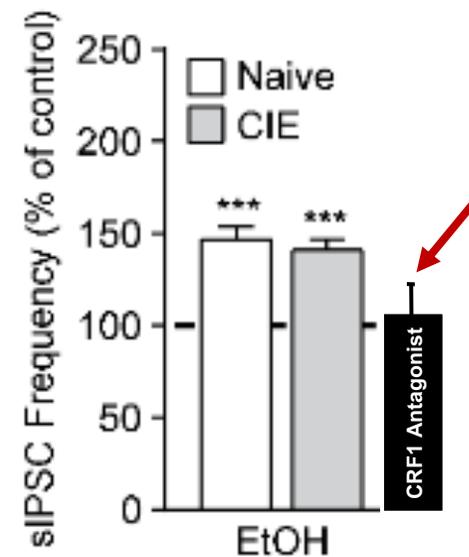
- CRF is the main physiological regulator of stress responses (Deussing & Chen, 2018) and plays a key role in AUD (Koob and Zorilla, 2010; Roberto et., 2017).
- CRF₁ antagonists reverse the negative emotional state and the excessive alcohol self-administration produced by AUD (Overstreet 2004; Funk 2007).



Alcohol Enhances CeA GABAergic Transmission in Rodents



Acute EtOH

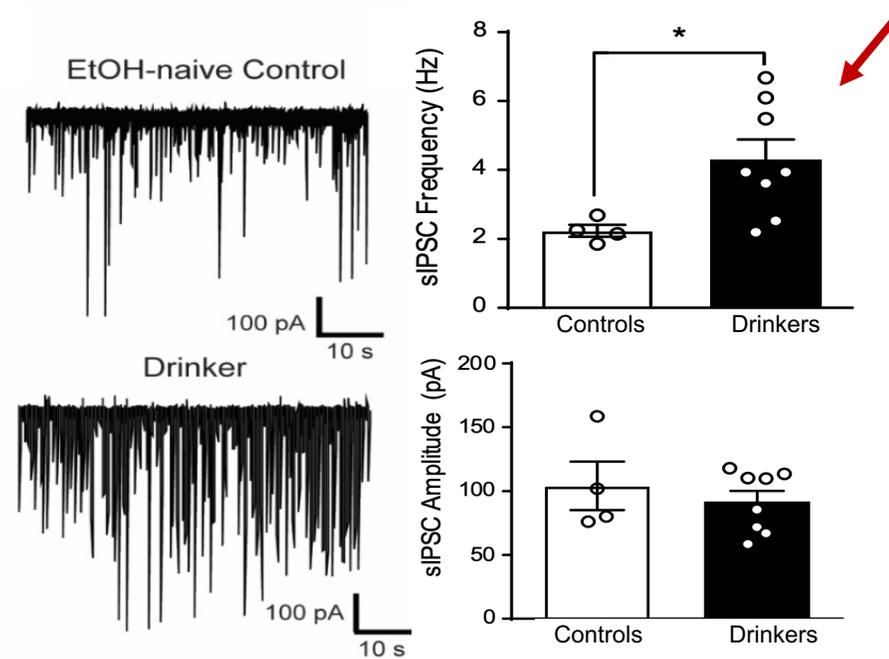


George R. Siggins
"Geobob"

Chronic Intermittent Ethanol Exposure = CIE = EtOH-Dependence

Roberto et al., 2003, PNAS; Roberto et al., 2004, J. Neurosci; Varodayan et al., 2017, J. of Neurosci

Alcohol Enhances CeA GABAergic Transmission In Non-Human Primates



Jimenez et al., 2019, NPP; Patel et al., 2021, NPP

In Collaboration with Oregon National Primate Research Center

INIA-Neuroimmune consortium



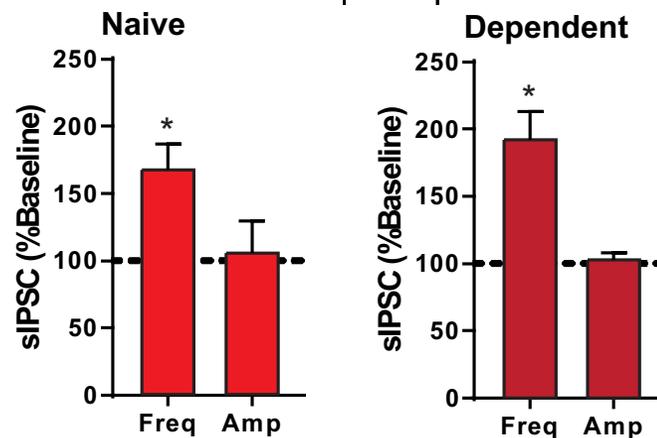
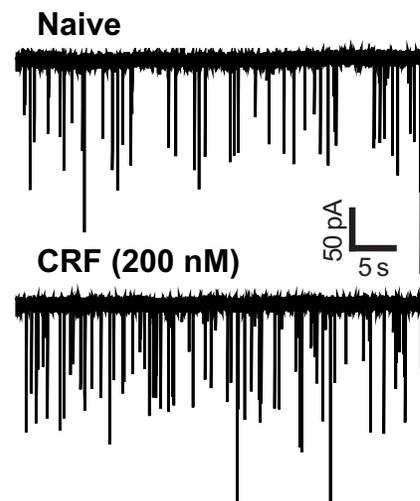
CRF Enhances CeA GABAergic Transmission



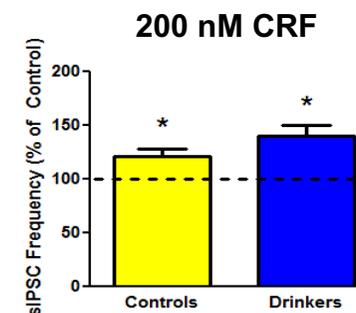
Larry
Rodriguez



Dean
Kirson



Non-Human Primate



Patel et al., 2021 NPP

In Collaboration with
Oregon National Primate Research Center

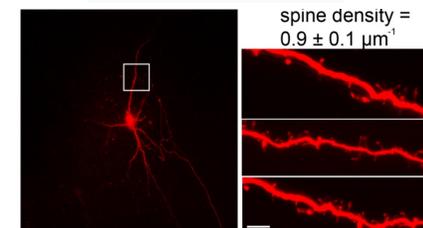
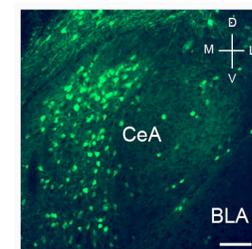
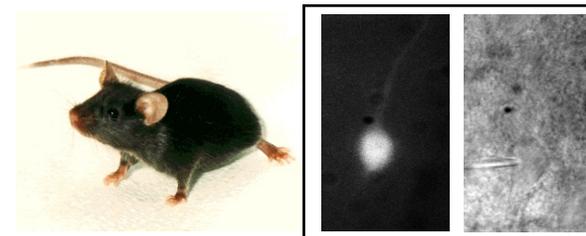
Roberto et al., 2010, *Biol. Psychiatry*
Varodayan et al., 2017, *J. Neurosci.*
Rodriguez, Kirson et al., 2022, *Int J Mol Sci.*



The Brain is Wired

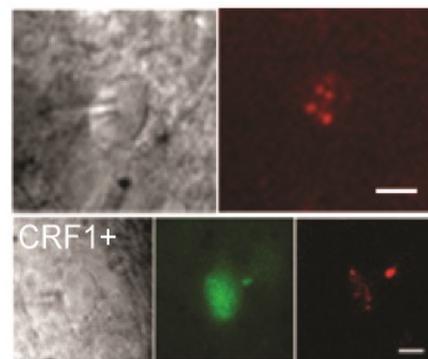
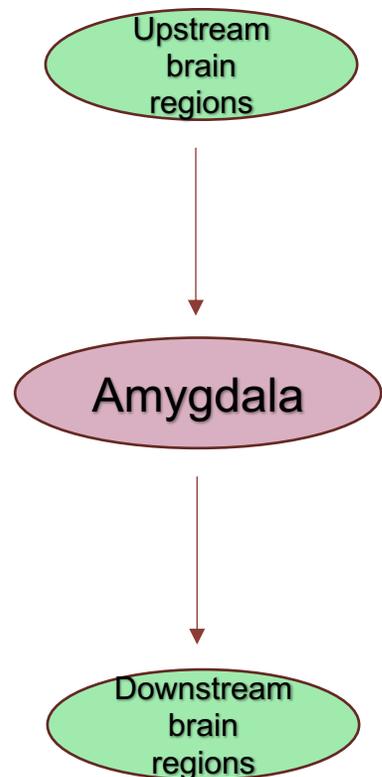


CRF₁ Microcircuitry



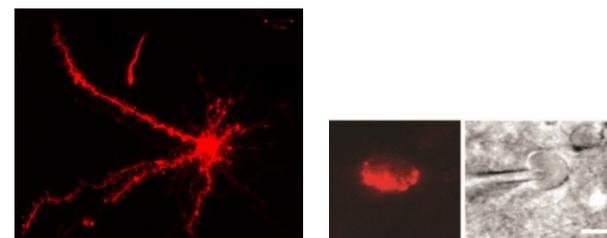
CRF1:GFP transgenic mice that express GFP under the control of CRF1 receptor gene promoter
Crh1:Cre mice
Crh-IRES-Cre mice

CRF₁ Amygdala Projections



Control

EtOH-Dep



Crh-IRES-Cre mice CeA injected with an AAV2-DIO-hM3Dq-mCherry vector

Herman et al., J. of Neurosci. 2013; Herman et al., J. of Neurosci. 2016; Kreifeldt, Herman et al., Mol. Psychiatry, 2022



Candice Contet



Melissa Herman

Cortical Amygdala Afferents



Gandhi et al., unpublished



Pauravi Gandhi



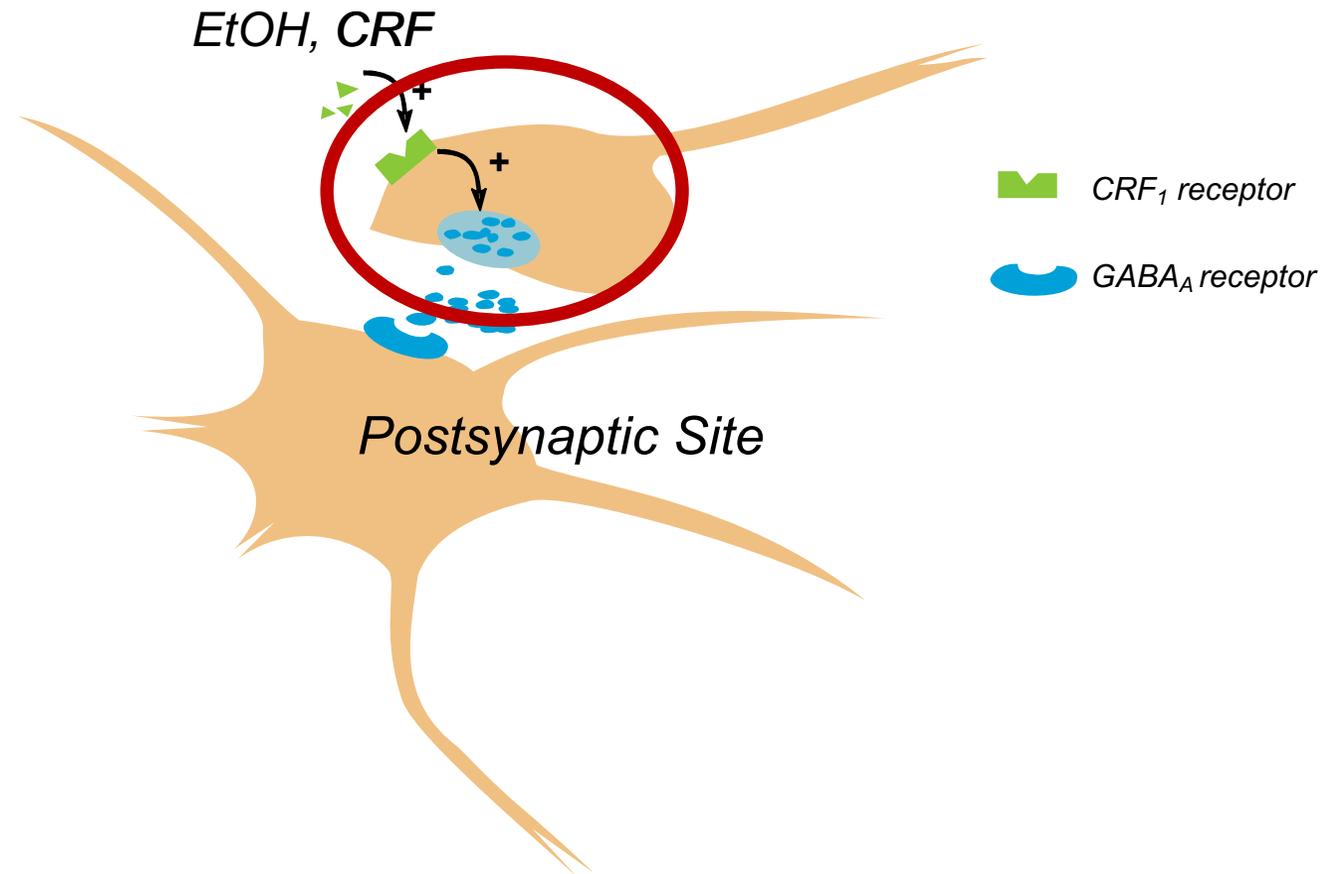
Roman Vkolinsky

Presynaptic Site

AD = imbalance
Physiological state = homeostasis



GABA
CRF



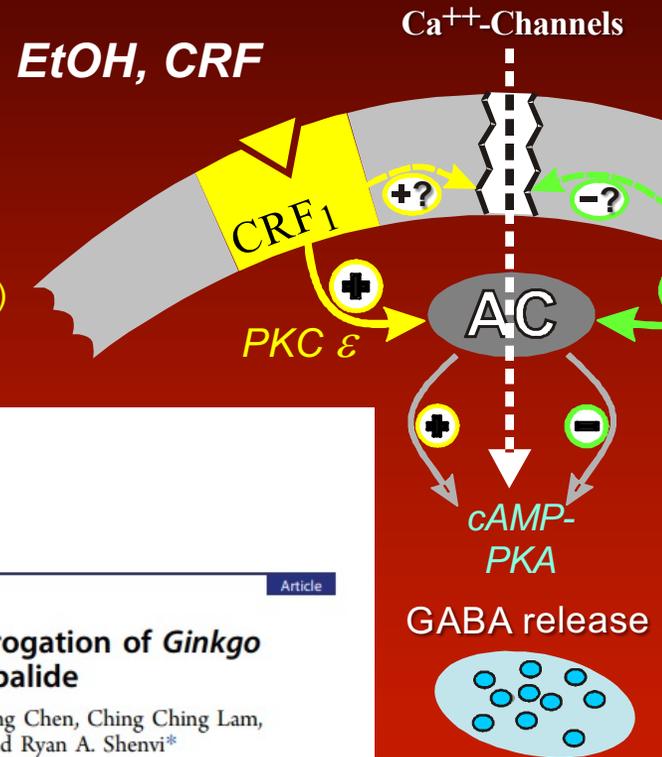
Molecular Mechanisms

Pro-stress:

Glucocorticoids
Noradrenaline
Serotonin
Substance P
PACAP-38
Hypocretin (orexin)

EtOH, CRF

Ca⁺⁺-Channels



Anti-Stress:

Endocannabinoids
Neuropeptide Y
Nociceptin
Opioids
Oxytocin



5762 • The Journal of Neuroscience, May 28, 2008 • 28(22):5762–5771

Behavioral/Systems/Cognitive

Cellular and Behavioral Interactions of Gabapentin with Alcohol Dependence

Marisa Roberto,^{1,3} Nicholas W. Gilpin,¹ Laura E. O'Dell,⁴ Maureen T. Cruz,¹ Andrew C. Morse,⁵ George R. Siggins,² and George F. Koob^{1,3}

¹Committee on the Neurobiology of Addictive Disorders, ²Department of Molecular and Integrative Neurosciences, and ³Pearson Center for Alcoholism and Addiction Research, The Scripps Research Institute, La Jolla, California 92037, ⁴Department of Psychology, University of Texas at El Paso, El Paso, Texas 79902, and ⁵BrainCells, San Diego, California 92121

Original Investigation

Gabapentin Treatment for Alcohol Dependence A Randomized Clinical Trial

Barbara J. Mason, PhD; Susan Quello, BA, BS; Vivian Goodell, MPH; Farhad Shadan, MD; Mark Kyle, MD; Adnan Begovic, MD

JAMA Intern Med. 2014;174(1):70-77. doi:10.1001/jamainternmed.2013.11950
Published online November 4, 2013.

J | A | C | S
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

pubs.acs.org/JACS

Article

Synthetic, Mechanistic, and Biological Interrogation of *Ginkgo biloba* Chemical Space En Route to (–)-Bilobalide

Robert M. Demoret,[▽] Meghan A. Baker,[▽] Masaki Ohtawa, Shuming Chen, Ching Ching Lam, Sophia Khom, Marisa Roberto, Stefano Forli, Kendall N. Houk, and Ryan A. Shenvi*

Cite This: *J. Am. Chem. Soc.* 2020, 142, 18599–18618

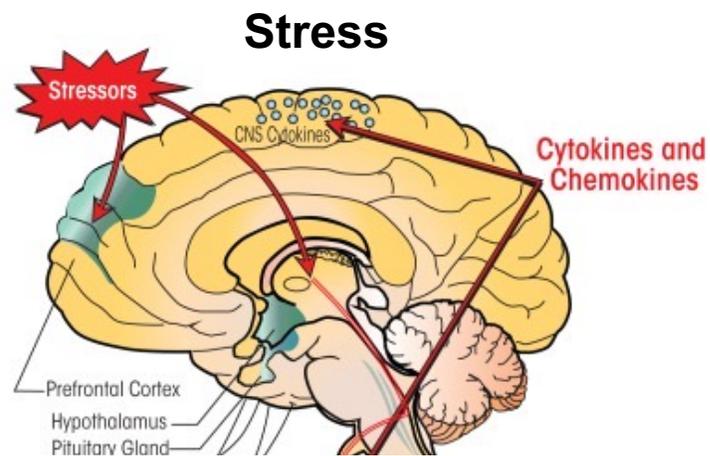
Read Online



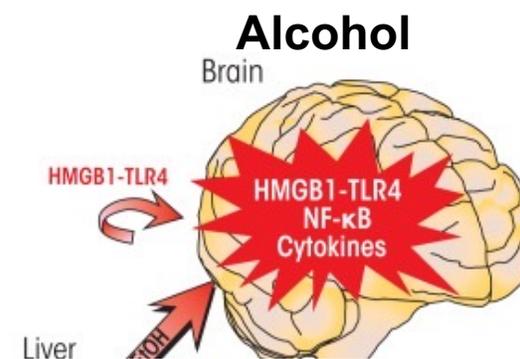
Summary: Recruitment of Stress Systems

Alcohol and the stress peptide CRF increase GABAergic release in the amygdala across species, pointing to the key translational role of this peptide.

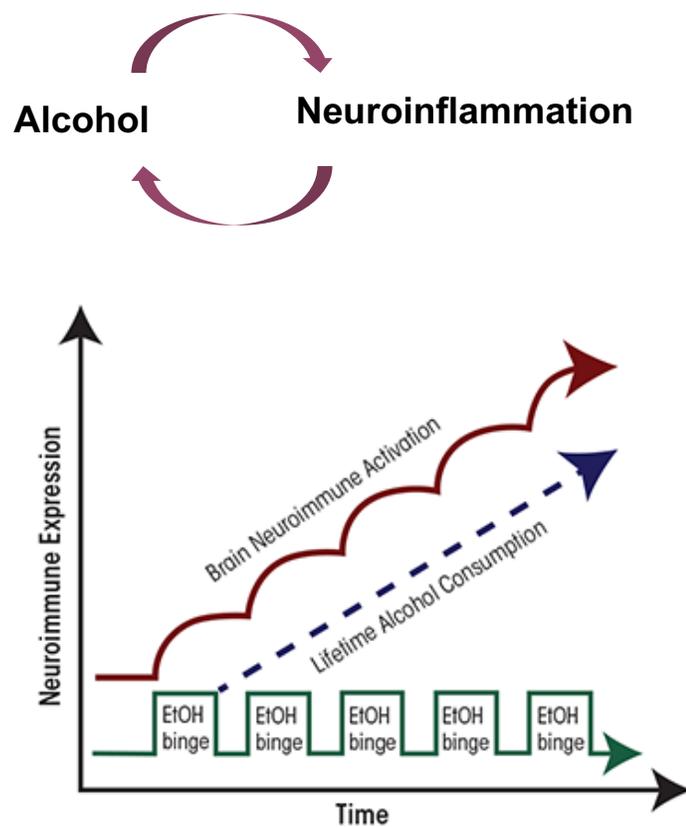
Normalizing this “compromised” GABA/CRF-transmission alleviate several aspects of AUD in preclinical and clinical studies.



Neuroimmune Signaling Integrates CNS Responses to Alcohol and Stress

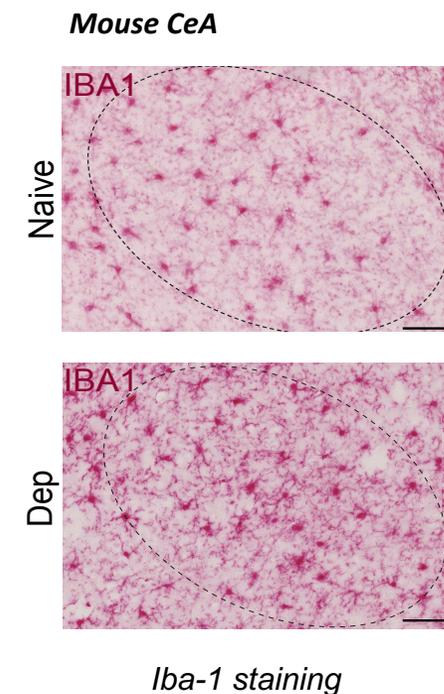


Alcohol-Neuroimmune Interactions are Complex



From: Crews et al., *Alcohol Res. Curr. Rev.* 37, 2015

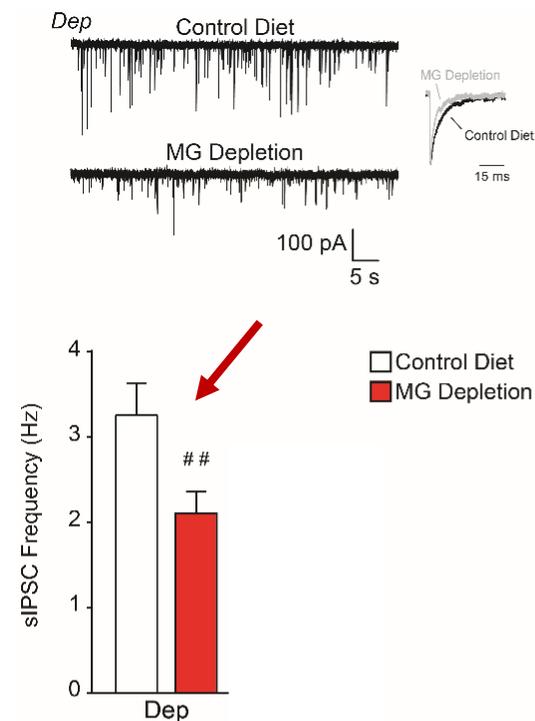
Chronic Alcohol Increases Inflammation By Activating Microglia



Warden et al., 2020, *Biological Psychiatry*

INIA-Neuroimmune consortium

Decreasing Inflammation “Normalizes” CeA GABAergic Transmission



Florence
Varodayan



Reesha
Patel



Sophia
Khom

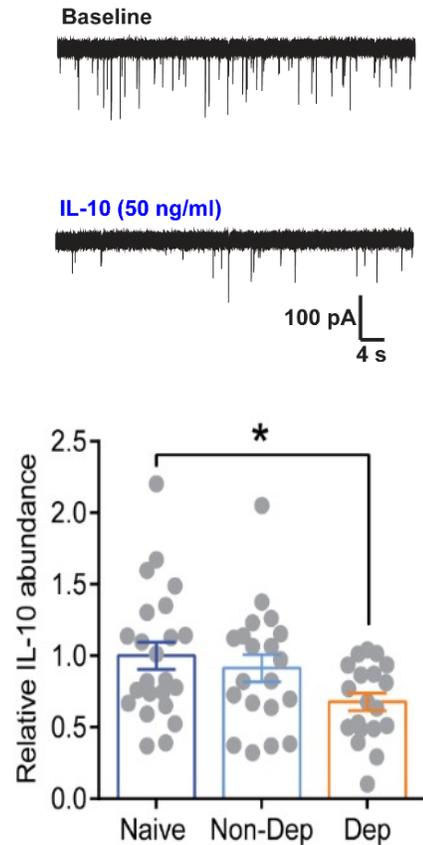
Microglia Depletion Treatment using PLX 5622 Diet (a colony stimulating factor 1 inhibitor)

INIA-Neuroimmune consortium

Anti-inflammatory Interleukin-10 (IL-10) is Decreased with Dependence



Reesha Patel



Published in final edited form as:

Prog Neurobiol. 2021 April ; 199: 101952. doi:10.1016/j.pneurobio.2020.101952.

IL-10 normalizes aberrant amygdala GABA transmission and reverses anxiety-like behavior and dependence-induced escalation of alcohol intake

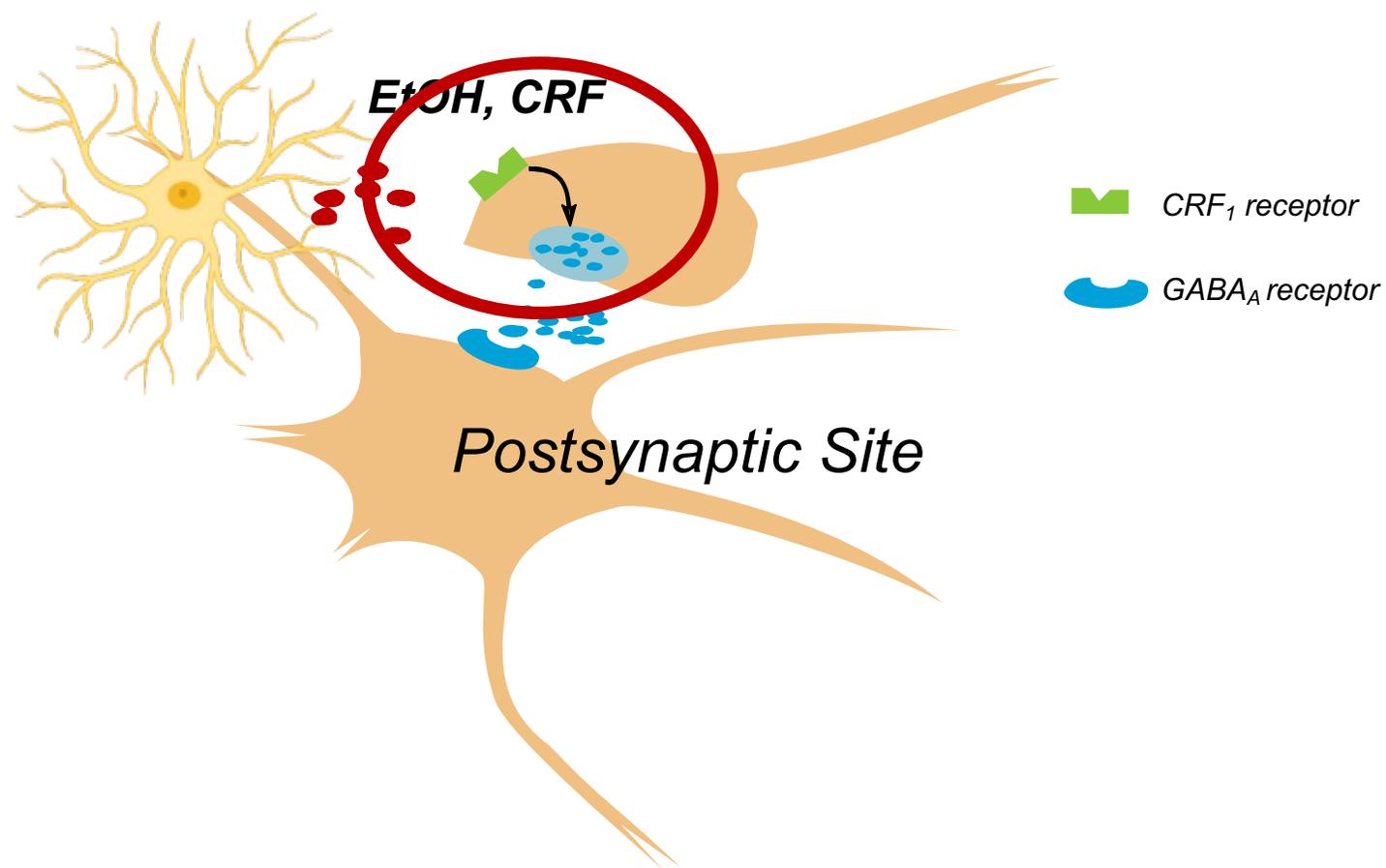
Reesha R. Patel¹, Sarah A. Wolfe¹, Michal Bajo¹, Shawn Abeynaike¹, Amanda Pahng^{2,3}, Vittoria Borgonetti¹, Shannon D'Ambrosio¹, Rana Nikzad¹, Scott Edwards², Silke Paust¹, Amanda J. Roberts¹, Marisa Roberto^{1,*}

¹The Scripps Research Institute, 10550 N. Torrey Pines Rd, La Jolla, CA 92037, USA

²Louisiana State University Health Sciences Center, 1901 Perdido St, New Orleans, LA 70112, USA

³Southeast Louisiana Veterans Health Care System, 2400 Canal Street, New Orleans, LA 70119, USA

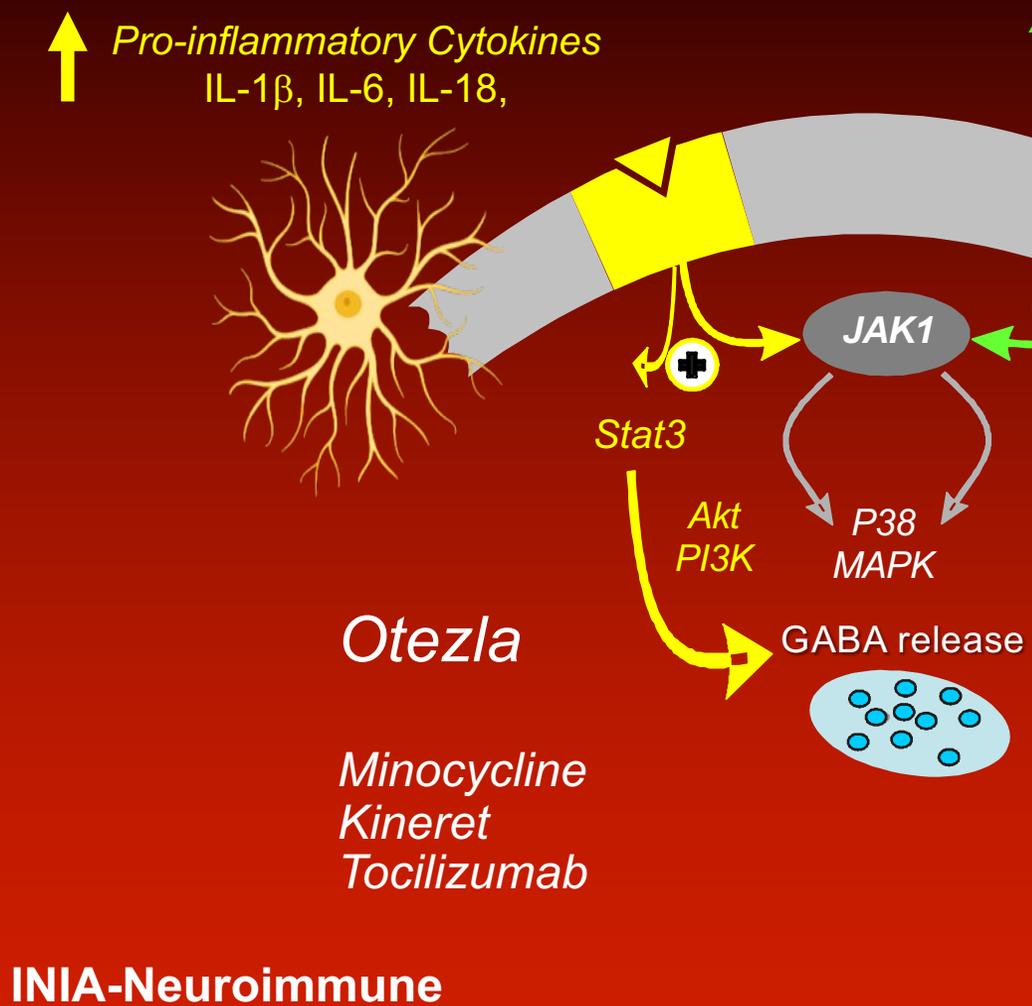
Presynaptic Site



AUD = imbalance



Molecular Mechanisms



CSH Cold Spring Harbor Laboratory

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

Rosetta Stone Approach

bioRxiv posts many COVID-19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

New Results [Follow this preprint](#)

The FDA-approved drug apremilast suppresses alcohol intake: clinical and pre-clinical validation

Kolter B. Grigsby, Regina A. Mangieri, Amanda J. Roberts, Marcelo F. Lopez, Alexander Tran, Evan J. Firsick, Kayla G. Townsley, Alan Beneze, Jessica Bess, Toby K. Eisenstein, Joseph J. Meissler, John M. Light, Jenny Miller, Susan Quello, Farhad Shadan, Michael Skinner, Heather C. Aziz, Pamela Metten, Richard A. Morissett, John C. Crabbe, Marisa Roberto, Howard C. Becker, Barbara J. Mason, Angela R. Ozburn
doi: <https://doi.org/10.1101/2021.05.13.444033>

This article is a preprint and has not been certified by peer review [what does this mean?].

INIA-Neuroimmune

Summary: Recruitment of Neuroimmune Systems

Components of immune systems (e.g., microglia and IL-10) contribute to increased GABA release.

Manipulating these targets ameliorates the cellular and behavioral phenotypes in animal models and individuals with AUD.

Take Away Message:

Understanding the neurobiology of AUD using preclinical models is a necessary step for screening potential therapeutics for this disease.

To take a drug from “the bench to the bedside” may be a long process.



The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has developed the Treatment Navigator as an online resource to learn about evidence-based treatment options and to locate a qualified treatment provider in your area or via telehealth.

The link to NIAAA's Treatment Navigator is <https://alcoholtreatment.niaaa.nih.gov>

How much alcohol is too much?

Visit the NIAAA website as an online resource to learn about guidelines for number of drinks.

The link to NIAAA's basic information is

<https://www.niaaa.nih.gov/health-professionals-communities/core-resource-on-alcohol/basics-defining-how-much-alcohol-too-much>



Acknowledgements

People

All **current** and **past** members of Roberto lab
Collaborators and Colleagues at Scripps and outside Scripps
The Scripps Core Facilities

Funding and Support

Schimmel Family Endowed Chair
NIH/National Institute of Alcohol Abuse and Alcoholism (NIAAA)
Integrative Neuroscience Initiative on Alcoholism (INIA)-Neuroimmune Consortium
NIAAA-TSRI-Alcohol Research Center P60
T32 Multidisciplinary Training
Pearson Center for Alcoholism and Addiction Research
Department of Defense (DoD)





Currently Available FDA Approved Medications

Disulfiram (Antabuse®)

Aldehyde Dehydrogenase
(FDA approval 1949)

Naltrexone (Revia®,
Depade®)

Primarily Mu Opioid Receptor
(FDA approval 1994)

Acamprosate (Campral®)

Glutamate and perhaps GABA- (FDA
approval 2004)

Naltrexone Depot (Vivitrol®)

Primarily Mu Opioid Receptor
(FDA approval 2006)



Advancing maternal health with digital technologies

Wednesday, September 21 | 1:00 pm PT/4:00 pm ET

Tolúwalàsé Ajayi, MD
*Director, Clinical Research and Diversity Initiatives
Scripps Research Translational Institute*



Hacking our body clocks to optimize health

Wednesday, October 19 | 1:00 pm PT/4:00 pm ET

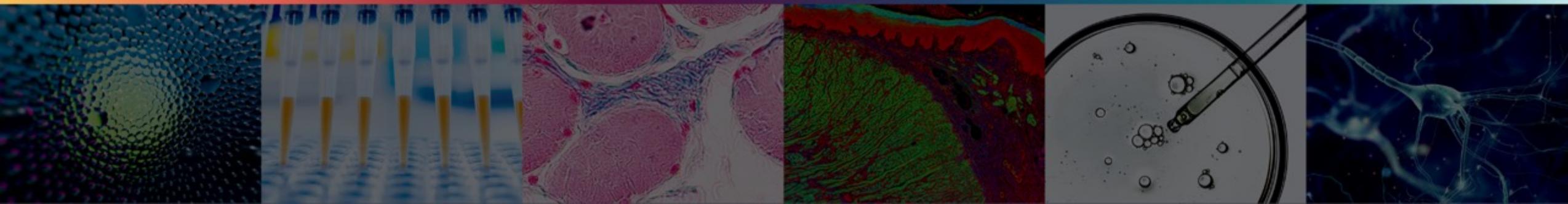
Katja Lamia, PhD
*Associate Professor
Department of Molecular Medicine*



Supercharging the immune system to destroy tumors

Wednesday, November 16 | 1:00 pm PT/4:00 pm ET

Silke Paust, PhD
*Associate Professor
Department of Immunology and Microbiology*



Science Changing Life.

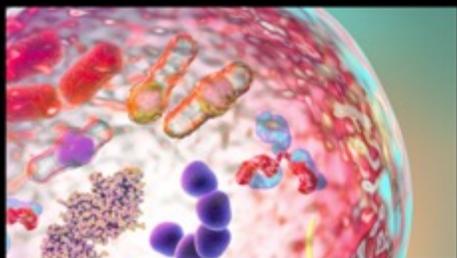
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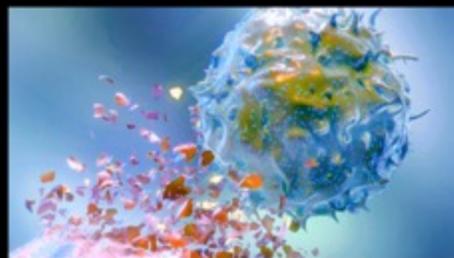
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Evert Njomen:
Hacking our cellular recycling system to prevent the next deadly pathogen



Episode 35
Andrew Su:
How artificial and community intelligence are shaping medicine



Episode 34
Travis Young:
Finding a cure for cancer with novel immunotherapies



SCAN ME