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
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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.
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.
An international influence.

Roberto has organized four editions of the International Congress on Alcoholism and Stress, helming 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.
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

<table>
<thead>
<tr>
<th>Disorder/Disease</th>
<th>Millions in the US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>14.4</td>
</tr>
<tr>
<td>Illicit drugs</td>
<td>6.6</td>
</tr>
<tr>
<td>Tobacco</td>
<td>28.6</td>
</tr>
<tr>
<td>Cancer</td>
<td>14.5</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Cost to society

<table>
<thead>
<tr>
<th>Disorder/Disease</th>
<th>$ Billions / year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>249</td>
</tr>
<tr>
<td>Illicit drugs</td>
<td>193</td>
</tr>
<tr>
<td>Tobacco</td>
<td>295</td>
</tr>
<tr>
<td>Cancer</td>
<td>217</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>36</td>
</tr>
</tbody>
</table>


NIH Budget

- Alcohol: 0.5
- Tobacco: 0.4
- Stim/opiate: 1
- Cancer: 5.5
- HIV/AIDS: 3.1

700 billion/year
• 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”

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

New Yorker cartoon

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

Volkow, Gordon, Koob, Neuropsychopharmacology, 2021
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

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.
Whole-cell voltage-clamp recordings of spontaneous and miniature GABA<sub>A</sub> inhibitory post-synaptic currents [sIPSCs and mIPSCs (in TTX)] in glutamate and GABA<sub>B</sub> 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

Basal

sIPSCs

Naive Rat

EtOH-Dep Rat

100 pA

10 s

Acute EtOH

sIPSC Frequency (Hz)

Naive CIE

***

sIPSC Frequency (% of control)

CIE Antagonist

Naive CIE

*** ***

EtOH

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

Naive

Dependent

Non-Human Primate

Patel et al., 2021 NPP

In Collaboration with Oregon National Primate Research Center

Roberto et al., 2010, Biol. Psychiatry
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
Crt1:Cre mice
Crt-IRESCre mice
**CRF₁ Amygdala Projections**

CRh-IRESCre mice CeA injected with an AAV2-DIO-hM3Dq-mCherry vector


**Cortical Amygdala Afferents**

Gandhi et al., unpublished
Physiological state = homeostasis

AUD = imbalance

GABA, CRF

Presynaptic Site

Postsynaptic Site

EtOH, CRF

CRF

GABA

CRF$_1$ receptor

GABA$_A$ receptor

CRF
Molecular Mechanisms

**Pro-stress:**

EtOH, CRF

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

**Anti-Stress:**

Endocannabinoids
Neuropeptide Y
Nociceptin
Opioids
Oxytocin

Cellular and Behavioral Interactions of Gabapentin with Alcohol Dependence

Marisa Roberto, Nicholas W. Gilpin, Laura E. O'Dell, Maureen T. Cruz, Andrew C. Morse, George R. Siggins, and George F. Koob

*Correspondence to the Neurobiology of Addictive Disorders, Department of Molecular and Integrative Neuroscience, and Pearson Center for Alcoholism and Addiction Research, The Scripps Research Institute, La Jolla, California 92037, Department of Psychology, University of Texas at El Paso, El Paso, Texas 79968, and Brain Cells, 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; Adrian Begovic, MD


Mason, B.J et al., 2018, Addiction Biology, Gabapentin for the treatment of alcohol use disorder
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.
Stress

Neuroimmune Signaling Integrates CNS
Responses to Alcohol and Stress

Alcohol-Neuroimmune Interactions are Complex

Chronic Alcohol Increases Inflammation By Activating Microglia


INIA-Neuroimmune consortium

Warden et al., 2020, Biological Psychiatry
Decreasing Inflammation “Normalizes” CeA GABAergic Transmission

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

INIA-Neuroimmune consortium

Warden, Wolfe et al., 2020, Biological Psychiatry
Anti-inflammatory Interleukin-10 (IL-10) is Decreased with Dependence

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 Abeynaika1, Amanda Pahng2,3, Vittoria Borgonetti1, Shannon D’Ambrosio1, Rana Nikzad1, Scott Edwards2, Silke Paust1, Amanda J. Roberts1, Marisa Roberto1

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

EtOH, CRF

CRF₁ receptor

GABAₐ receptor

AUD = imbalance

Postsynaptic Site
Molecular Mechanisms

**Pro-inflammatory Cytokines**
- IL-1β, IL-6, IL-18,

**Anti-inflammatory Cytokines**
- IL-10, IL-1ra, IL-18bp

**Otezla**

**INIA-Neuroimmune**

**Rosetta Stone Approach**

**INIA-Neuroimmune**

Huang et al., 2021 ACER. Network Meta-analysis on the Mechanisms Underlying Alcohol Augmentation of COVID-19 Pathologies
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)
<table>
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<tr>
<th>Medication</th>
<th>Target</th>
<th>FDA Approval Date</th>
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</thead>
<tbody>
<tr>
<td>Disulfiram (Antabuse®)</td>
<td>Aldehyde Dehydrogenase</td>
<td>1949</td>
</tr>
<tr>
<td>Naltrexone (Revia®, Depade®)</td>
<td>Primarily Mu Opioid Receptor</td>
<td>1994</td>
</tr>
<tr>
<td>Acamprosate (Campral®)</td>
<td>Glutamate and perhaps GABA-</td>
<td>2004</td>
</tr>
<tr>
<td>Naltrexone Depot (Vivitrol®)</td>
<td>Primarily Mu Opioid Receptor</td>
<td>2006</td>
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Advancing maternal health with digital technologies  
**Wednesday, September 21 | 1:00 pm PT/4:00 pm ET**

Tokúwalâse 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
Podcast
New episodes available to stream now!

Episode 36
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