## Research Projects - concluded

### Concluded Extend and Confirm Projects funded by the ITN

<table>
<thead>
<tr>
<th><strong>Translational Mouse Models of PTSD and Comorbid Substance Use</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principal Investigator(s):</strong> Eric R. Kandel, M.D.</td>
<td>[1]</td>
</tr>
<tr>
<td><strong>Columbia University</strong></td>
<td>[2]</td>
</tr>
<tr>
<td><strong>Lay Abstract</strong></td>
<td>Identify causal biological mechanisms of PTSD using a novel gene x environment mouse model of stress vulnerability, and characterize the interaction between PTSD-like symptoms and nicotine/alcohol consumption. Identify SNPs associated with PTSD, or PTSD and comorbid substance use disorders, informed by our mouse model. Examine the genetics and epidemiology of substance abuse among men and women separately in a large military sample, informed by our mouse model.</td>
</tr>
<tr>
<td><strong>Keywords</strong></td>
<td>mouse model, stress vulnerability, TIA-1 SNPs</td>
</tr>
<tr>
<td><strong>Date concluded</strong></td>
<td>7/31/2016</td>
</tr>
<tr>
<td><strong>Treatment Type</strong></td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Target population</strong></td>
<td>Mouse Studies</td>
</tr>
<tr>
<td><strong>IND</strong></td>
<td>n/a</td>
</tr>
</tbody>
</table>

### Oxytocin Suppresses Substance Use Disorders Associated with Chronic Stress

<table>
<thead>
<tr>
<th><strong>Principal Investigator(s):</strong> Jacqueline F. McGinty, Ph.D.</th>
<th>[3]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical University of South Carolina</strong></td>
<td>[4]</td>
</tr>
<tr>
<td><strong>Lay Abstract</strong></td>
<td>Study/Product Aim(s): Demonstrate effects of systemic oxytocin or carbetocin administration on reinstatement of meth seeking and epigenetic adaptations in the brain of rats after chronic stress. Demonstrate effects of systemic oxytocin or carbetocin administration on reinstatement of ethanol seeking and epigenetic adaptations in the brain of mice after chronic stress. Demonstrate effects of intra-nasal oxytocin administration on PTSD symptoms and substance use of dual-diagnosed veterans.</td>
</tr>
<tr>
<td><strong>Keywords</strong></td>
<td>animal studies, meth addiction, alcohol abuse, PTSD</td>
</tr>
<tr>
<td><strong>Date concluded</strong></td>
<td>6/30/2016</td>
</tr>
</tbody>
</table>
Pharmacological: Oxytocin (intranasal) & Carbetocin

Rat Studies

This study has an active IND

Concluded Proof of Principle Projects funded by ITN

Restoration of glial glutamate transport to prevent posttraumatic stress and vulnerability to alcohol and marijuana use and relapse
Principal Investigator(s): Peter W. Kalivas, Ph.D. [5]
Medical University of South Carolina [4]

Although we used NAC in a pilot study with success in treating Veterans with comorbid PTSD/SUDs, it is unknown if using NAC either prophylactically, or immediately after a stressful experience can prevent vulnerability to developing PTSD or comorbid PTSD/SUDs. We propose preclinical validation for the use of NAC prophylactically or immediately post-­combat stress to reduce the neurological sequelae that establishes PTSD and PTSD/SUDs comorbidity. 1) We have expanded the validity of the animal model by associating an odor with the immobilization stress, and we use exposure to the odor to provoke relapse (reinstated lever pressing) in animals trained to self-administer drug. 2) We will treat rats with N-­acetylcysteine either during or immediately after exposure to immobilization stress, and determine if this prevents stress-­induced augmented acquisition of drug self-­administration and the capacity of the stress-­associated odor to reinstate drug seeking. Simultaneously, we will validate that NAC has normalized EAAT2 levels, a key neurological action of NAC?s protective effects. 3) We recently developed an animal model of rat i.v. self-­administration and reinstatement of the key constituents of marijuana, ?9-­?-­tetrahydrocannabinol and cannabidiol. Marijuana abuse is a substantially larger problem in Veterans with comorbid PTSD and SUDs than cocaine abuse, making use of this model for the determining the biological basis of PTSD/SUDs comorbidity more clinically relevant.

Keywords
PTSD, SUDs, Marijuana Abuse, Stress, Prevention, Glutamate transport, N-­acetylcysteine

Recruiting
n/a

NAC

Rat Studies
Neuroprotection Against Alcohol Neurotoxicity and Traumatic Brain Injury in a Cerebellar Slice Model


Lay Abstract

Task #1: To establish a model of focal mechanical injury to cultured cerebellar slices from young adult mice. Task #2: To determine whether ethanol potentiates the effects of TBI. Task #3: To determine whether NAP protects against the effects of TBI, ethanol exposure, or both.

Keywords
alcohol abuse, TBI, NAP, mouse studies

Recruiting
n/a

Treatment Type
Pharmacological: NAPVSIPQ (NAP)

Target Population
Mouse Studies

IND
n/a

Topiramate Treatment of Hazardous and Harmful Alcohol Use in Veterans with TBI

Principal Investigator(s): Steven L. Batki, M.D [8]. Northern California Institute for Research and Education [9]

Lay Abstract

The project aims to: 1) Obtain a preliminary assessment of the effectiveness of topiramate in reducing alcohol use and TBI symptoms in veterans with TBI and hazardous or harmful alcohol use; 2) Assess the safety/tolerability of topiramate in these patients; 3) Assess the feasibility of recruitment/retention for topiramate treatment; and 4) To inform the design of a planned subsequent larger controlled trial of topiramate.

Keywords
alcohol abuse, topirimate, mTBI, veterans, pharmacotherapy, co-occurring disorders, topiramate

Date concluded
10/31/2015

Treatment Type
Pharmacologic: Toprimate

Target Population
Veterans with TBI and AUD

IND
exempt
Animal models of binge drinking and PTSD: novel therapeutic targets and pharmacological interventions from gene expression profiles
Principal Investigator(s): John C. Crabbe, Ph.D. [15]
Oregon Health & Science University [16]

### Lay Abstract

Study/Product Aims:  
- Employ HDID binge drinking mice to test novel compounds for efficacy to reduce drinking  
- Provide brain tissue from HDID mice to Texas to discover novel compounds for testing  
- Use PTSD-like assay to exacerbate binge drinking in HDID mice

Keywords  
- alcohol; binge drinking; posttraumatic stress disorder; genetics; pharmacotherapy

Date concluded  
- 12/31/2013

Treatment Type  
- Pharmacological: tezaglitazer, fenofibrate

Target Population  
- Mouse Studies (HDID)

### IND

- n/a

### Related Publications
- Selection for drinking in the dark alters brain gene coexpression networks [17]
- Genetic influences on addiction [18]
- Rodent models of genetic contributions to motivation to abuse alcohol [19]
- Progress in a Replicated Selection for Elevated Blood Ethanol Concentrations in HDID Mice [20]
- High drinking in the dark mice: a genetic model of drinking to intoxication [21]
- Genotypic and sex differences in anxiety-like behavior and alcohol-induced anxiolysis in High Drinking in the Dark selected mice [22]
- Rewarding and aversive effects of ethanol in High Drinking in the Dark selectively bred mice [23]
- Behavioral Genetics of the Mouse [24]
Catechol-O-Methyltransferase, Impulsivity and Substance Abuse Treatment
Principal Investigator(s): Howard L. Fields, M.D., Ph.D. [25] and Andrew Kayser, M.D., Ph.D. [26]
Ernest Gallo Clinic and Research Center [27]

Lay Abstract
Determine whether tolcapone will preferentially reduce impulsivity in individuals with the val/val 158 genotype and produce commensurate changes in CNS circuits involved in intertemporal choice. Determine whether entacapone will preferentially reduce impulsivity in individuals with the val/val 158 genotype and produce commensurate changes in CNS circuits involved in intertemporal choice. Determine whether the effect of COMT inhibitors on impulsivity depends upon their ability to cross the blood brain barrier.

Keywords
tolcapone, impulsivity, COMT inhibitors

Date concluded 6/30/2016

Treatment Type Pharmacological: tolcapone & entacapone (COMT inhibitors)

Target Population Civilians

IND not required
- Right inferior frontal cortex activity correlates with tolcapone responsivity in problem and pathological gamblers [28]
- Dopamine, Locus of Control, and the Exploration Exploitation Tradeoff [29]
- Dopamine, Corticostriatal Connectivity, and Intertemporal Choice [30]
- Dopamine Modulates Egalitarian Behavior in Humans [31]
- A neural correlate of strategic exploration at the onset of adolescence [32]

Animal models of binge drinking and PTSD: novel therapeutic targets and pharmacological interventions from gene expression profiles
Principal Investigator(s): R. Adron Harris, Ph.D. [33]
The University of Texas at Austin [34]

Lay Abstract
The overall goal of this work is to combine genomic and behavioral approaches to repurpose approved medications that can provide new and effective treatments for combined binge drinking and PTSD.

Keywords
alcohol; binge drinking; posttraumatic stress disorder; genetics; pharmacotherapy

Date concluded 12/31/2013

Treatment Type Genetics studies looking for drug targets

Target Population Mouse and rat studies
The INIA Texas Gene Expression Database (IT-GED): An online tool for alcohol genomics [35]

Epigenetic control of gene expression in the alcoholic brain [36]

Gene expression in brain and liver produced by three different regimens of alcohol consumption in mice: comparison with immune activation [37]

The role of transposable elements in health and diseases of the central nervous system [38]

Proteomic approaches and identification of novel therapeutic targets for alcoholism [39]

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**Glial regulators for treating comorbid post-traumatic stress disorder (injury) and substance abuse disorders**

Principal Investigator(s): Peter W. Kalivas, Ph.D. [5]

*Medical University of South Carolina* [4]

<table>
<thead>
<tr>
<th>Lay Abstract</th>
<th>Study/Product Aim(s): ? Establish a proof-of-concept clinical trial protocol for measuring drug craving and relapse in Veterans with comorbid PTSD and substance use disorders (SUDs). ? Determine the efficacy and safety of N-acetylcysteine in preventing relapse and reducing drug craving and PTSD symptoms among Veterans with comorbid PTSD and SUDs. This comorbidity is currently not effectively treated.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Keywords</strong></td>
<td>PTSD. Glia, stress, plasticity, addiction, Prefrontal cortex, cocaine, N-acetylcysteine; glutamate</td>
</tr>
<tr>
<td><strong>Date concluded</strong></td>
<td>6/30/2014</td>
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<tr>
<td><strong>Treatment Type</strong></td>
<td>Pharmacological: NAC</td>
</tr>
<tr>
<td><strong>Target population</strong></td>
<td>Veterans (with PTSD/SUD)</td>
</tr>
<tr>
<td><strong>IND</strong></td>
<td>no IND required</td>
</tr>
</tbody>
</table>

- A Double-Blind Randomized Controlled Pilot Trial of N-Acetylcysteine in Veterans with PTSD and Substance Use Disorders [40]

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**A translational epidemiological approach to the molecular basis of PTSD and substance abuse comorbidity**

Principal Investigator(s): Eric R. Kandel, M.D. [1]

*Columbia University* [2]
Study/Product Aim(s): Identify causal biological mechanisms of PTSD using a novel gene x environment mouse model of stress vulnerability, and characterize the interaction between PTSD-like symptoms and nicotine/alcohol consumption. Identify SNPs associated with PTSD, or PTSD and comorbid substance use disorders, informed by our mouse model. Examine the epidemiology of substance abuse among men and women separately in a large military sample, informed by our mouse model.

Keywords
PTSD, substance use disorders, male and female military personnel, animal models, causal molecular mechanisms, gateway sequence, nicotine, alcohol

Date concluded 9/30/2013

Treatment Type n/a

Target population n/a

IND n/a

- Gender differences in the expression of PTSD symptoms among active duty military personnel
- Posttraumatic Stress Disorder, Substance Abuse, and Other Behavioral Health Indicators among Active Duty Military Men and Women

Development of an animal model & novel treatments for comorbid PTSD and cocaine addiction
Principal Investigator(s): Lori A. Knackstedt, Ph.D.
University of Florida

Lay Abstract
Aim 1. Will treatment with an AT1R antagonist or ACE inhibitor after a traumatic event prevent the expression of symptoms of PTSD? Aim 2. Will therapy with an AT1R blocker or ACE inhibitor reduce cocaine seeking in an animal model of comorbid PTSD and cocaine addiction? Aim 3: Will therapy with an AT1R blocker or ACE inhibitor reduce methamphetamine-seeking in an animal model of comorbid PTSD and methamphetamine addiction?

Keywords
PTSD, Cocaine, Substance Use Disorder, Animal Model, Addiction, Angiotensin, Captoril, Candesartan

Date concluded 8/31/2016

Treatment Type Substance Abuse: Cocaine

Target population Rat Studies
Conditioned stress prevents cue-primed cocaine reinstatement only in stress-responsive rats [45]

Epigenetic modulation of interactions between fear and substance abuse
Principal Investigator(s): Kennon M. Lattal, Ph.D. [46]
Oregon Health & Science University [16]

Lay Abstract
Study/Product Aim(s): To determine whether potentiation of extinction by an HDAC3 inhibitor in a rodent model of PTSD weakens the ability of cues associated with trauma to cause relapse of drug seeking. To determine whether potentiation of extinction of drug seeking by an HDAC3 inhibitor protects extinguished drug seeking from reinstatement induced by cues associated with trauma.

Keywords
substance abuse, fear conditioning, HDAC3 inhibitor, RGFP966, extinction of fear

Date concluded
9/30/2014

Treatment Type
Pharmacologic: HDAC3 Inhibitor called RGFP966

Target population
Mouse and rat studies

IND
n/a

- G Protein-Gated Inwardly Rectifying Potassium Channel Subunit 3 Knock-Out Mice Show Enhanced Ethanol Reward [47]
- Chapter Three: Histone-Mediated Epigenetics in Addiction [48]
- Substance abuse, memory, and post-traumatic stress disorder [49]
- Acute ethanol withdrawal impairs contextual learning and enhances cued learning [50]
- Epigenetics and memory: causes, consequences and treatments for post-traumatic stress disorder and addiction [51]
- Opposing effects of D-cycloserine on fear despite a common extinction duration: interactions between brain regions and behavior [52]
- Delay and trace fear conditioning in C57BL/6 and DBA/2 mice: issues of measurement and performance [53]
- Activation of D1/5 Dopamine Receptors: A Common Mechanism for Enhancing Extinction of Fear and Reward-Seeking Behaviors [54]

Endogenous Modulators Suppress Substance Abuse Disorders Associated with Chronic Stress
<table>
<thead>
<tr>
<th>Lay Abstract</th>
<th>Study/Product Aim(s): ? Establish a preclinical model of PTSD vulnerability to methamphetamine (METH) self administration and seeking. ? Demonstrate effects of oxytocin and carbetocin on reinstatement of meth seeking after chronic stress. ? Examine neurobiological and epigenetic adaptations in the brains of METH seeking rats pre-exposed to chronic stress and treated with oxytocin or carbetocin.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keywords</td>
<td>Treatment Development</td>
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<tr>
<td>Date concluded</td>
<td>12/31/2013</td>
</tr>
<tr>
<td>Treatment Type</td>
<td>Pharmacological: oxytocin</td>
</tr>
<tr>
<td>Target population</td>
<td>PTSD model Rats studies</td>
</tr>
<tr>
<td>IND</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Effects of oxytocin on methamphetamine-seeking exacerbated by predator odor pre-exposure in rats [55]</td>
</tr>
</tbody>
</table>

**Oxytocin Suppresses Alcohol Drinking and Relapse in Mice**
Principal Investigator(s): Jacqueline F. McGinty, Ph.D. [3]
*Medical University of South Carolina* [4]

<table>
<thead>
<tr>
<th>Lay Abstract</th>
<th>Study/Product Aim(s): Determine the effects of oxytocin treatment on alcohol consumption in mice using a binge model of drinking. Determine the effects of oxytocin treatment on alcohol responding, consumption, and relapse behavior in mice.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keywords</td>
<td>oxytocin, binge-like alcohol drinking, mouse models, relapse</td>
</tr>
<tr>
<td>Date concluded</td>
<td>8/31/2015</td>
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<tr>
<td>Treatment Type</td>
<td>Pharmacological: Oxytocin</td>
</tr>
<tr>
<td>Target population</td>
<td>Mouse Studies</td>
</tr>
<tr>
<td>IND</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Oxytocin Reduces Ethanol Self-Administration in Mice [56]</td>
</tr>
</tbody>
</table>
### N-Type Calcium Channel Blockers for PTSD and Alcohol Use Disorders

**Principal Investigator(s):** Robert O. Messing, M.D.  \[57\]

**Ernest Gallo Clinic and Research Center** \[27\]

<table>
<thead>
<tr>
<th>Lay Abstract</th>
<th>Study/Product Aims; 1. Determine if drugs that inhibit N-type calcium channels reduce PTSD-like behavior in rats. 2. Determine if inhibitors of N-type calcium channels reduce operant ethanol self-administration and stress-induced reinstatement of ethanol seeking.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Keywords</strong></td>
<td>PTSD, alcohol abuse, rat studies, lomerizine, Z160, N-type Calcium channel blockers</td>
</tr>
<tr>
<td><strong>Date concluded</strong></td>
<td>6/30/2013</td>
</tr>
<tr>
<td><strong>Treatment Type</strong></td>
<td>Pharmacological: Lomerizine &amp; Z160</td>
</tr>
<tr>
<td><strong>Target population</strong></td>
<td>Rat studies</td>
</tr>
<tr>
<td><strong>IND</strong></td>
<td>n/a</td>
</tr>
</tbody>
</table>

### Zonisamide and CPT for veterans with PTSD and comorbid alcohol dependence

**Principal Investigator(s):** Ismene L. Petrakis, M.D.  \[58\]

**Yale University** \[59\]

<table>
<thead>
<tr>
<th>Lay Abstract</th>
<th>Hypothesis: We hypothesize that zonisamide will be more effective than placebo when used in combination of E-CPT-C in 1.) reducing heavy drinking days measured by the Timeline Follow-back Method (TLFB) 2.) reducing drinks per week as measured by the Timeline Follow-back Method (TLFB), 3.) reducing craving for alcohol using the Obsessive Compulsive Drinking Scale (OCDS).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Keywords</strong></td>
<td>treatment, pharmacotherapy, alcohol dependence, PTSD, zonisamide, cognitive processing therapy, alcohol use disorders</td>
</tr>
<tr>
<td><strong>Date concluded</strong></td>
<td>6/30/2015</td>
</tr>
<tr>
<td><strong>Treatment Type</strong></td>
<td>Pharmacologic and Cognitive Processing Therapy Combo: Zonisamide</td>
</tr>
<tr>
<td><strong>Target population</strong></td>
<td>Veterans with PTSD and AUD</td>
</tr>
<tr>
<td><strong>IND</strong></td>
<td>exempt</td>
</tr>
</tbody>
</table>
### Heat Shock Protein 90 at the Intersection of Alcohol Abuse and Stress: Preclinical Studies

**Principal Investigator(s):** Dorit Ron, Ph.D. [60]

**University of California, San Francisco** [61]

<table>
<thead>
<tr>
<th>Lay Abstract</th>
<th>Study Aim: ? Confirm our hypothesis stating that HSP90 is a focal shared contributor to mechanisms underlying alcohol abuse and stress ? Test pharmacotherapies at the preclinical level to decrease stress-induced behavior.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keywords</td>
<td>alcohol abuse, alcohol relapse, HSP90 inhibitor, NVP-AUY922</td>
</tr>
<tr>
<td>Date concluded</td>
<td>6/30/2014</td>
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<tr>
<td>Treatment Type</td>
<td>Pharmacologic: HSP90 inhibitor</td>
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<tr>
<td>Target population</td>
<td>Rat studies</td>
</tr>
<tr>
<td>IND</td>
<td>n/a</td>
</tr>
</tbody>
</table>

### Role of extended amygdala corticotropin-releasing factor and dynorphin brain systems in post-trauma ethanol use disorders

**Principal Investigator(s):** Eric P. Zorrilla, Ph.D. [62]

**The Scripps Research Institute** [63]

<table>
<thead>
<tr>
<th>Lay Abstract</th>
<th>Study/Product Aim(s) Task #1: To characterize post-stress and post-ethanol adverse ethanol use in the rat vis-à-vis compulsiveness and relapse. Task #2: To relate overactivation markers in CRF-CRF1 or dynorphin-KOR brain stress system to poor ethanol use outcomes Task #3: To inhibit CRF-CRF1 or dynorphin-KOR stress systems to reverse poor post-stress ethanol use outcomes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keywords</td>
<td>PTSD, relapse, corticotropin-releasing factor, kappa opioid receptor, alcoholism, ethanol reinforcement, dynorphin, self-administration behavior</td>
</tr>
<tr>
<td>Date concluded</td>
<td>10/24/2014</td>
</tr>
<tr>
<td>Treatment Type</td>
<td>Pharmacological: inhibition of the CRF-CRF1 or dynorphin-KOR stress systems (pexacerfont or CYM-50202)</td>
</tr>
<tr>
<td>Target population</td>
<td>Rat studies</td>
</tr>
<tr>
<td>IND</td>
<td>n/a</td>
</tr>
</tbody>
</table>