Research Projects - concluded

Concluded Extend and Confirm Projects funded by the ITN

Translational Mouse Models of PTSD and Comorbid Substance Use
Principal Investigator(s): Eric R. Kandel, M.D. [1]
Columbia University [2]

Lay Abstract
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.

Keywords
mouse model, stress vulnerability, TIA-1 SNPs

Date concluded 7/31/2016

Treatment Type n/a

Target population Mouse Studies

IND n/a

Oxytocin Suppresses Substance Use Disorders Associated with Chronic Stress
Principal Investigator(s): Jacqueline F. McGinty, Ph.D. [3]
Medical University of South Carolina [4]

Lay Abstract
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.

Keywords
animal studies, meth addiction, alcohol abuse, PTSD

Date concluded 6/30/2016
<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Pharmacological: Oxytocin (intranasal) &amp; Carbetocin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target population</td>
<td>Rat Studies</td>
</tr>
<tr>
<td>IND</td>
<td>This study has an active IND</td>
</tr>
</tbody>
</table>

**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]

| Lay Abstract | 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 |
| Treatment Type | NAC |
| Target Population | Rat Studies |
Neuroprotection Against Alcohol Neurotoxicity and Traumatic Brain Injury in a Cerebellar Slice Model

Principal Investigator(s): Michael E. Charness, M.D. [6]  
Boston VA Research Institute [7]

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
Relations Between Cognitive Functioning and Alcohol Use, Craving, and Post-Traumatic Stress: An Examination Among Trauma-Exposed Military Veterans With Alcohol Use Disorder [10]

An examination of relations between cognitive functioning and alcohol use and craving among veterans with alcohol use disorder and trauma exposure [11]

Topiramate treatment of alcohol use disorder in veterans with posttraumatic stress disorder: a randomized controlled pilot trial [12]

Alcohol use disorder and PTSD severity in veterans with and without comorbid TBI: Baseline subject characteristics in topiramate treatment trials [13]

Toward personalized medicine in the pharmacotherapy of alcohol use disorder: targeting patient genes and patient goals [14]

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

- 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., and Andrew Kayser, M.D., Ph.D.

**Ernest Gallo Clinic and Research Center**

| 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.

**The University of Texas at Austin**

| 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]

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]

Lay Abstract
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.

Keywords
PTSD. Glia, stress, plasticity, addiction, Prefrontal cortex, cocaine, N-acetylcysteine; glutamate

Date concluded 6/30/2014

Treatment Type Pharmacological: NAC

Target population Veterans (with PTSD/SUD)

IND no IND required

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

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]
Lay Abstract
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 [41]
- Posttraumatic Stress Disorder, Substance Abuse, and Other Behavioral Health Indicators among Active Duty Military Men and Women [42]

Development of an animal model & novel treatments for comorbid PTSD and cocaine addiction
Principal Investigator(s): Lori A. Knackstedt, Ph.D. [43]
University of Florida [44]

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
Lay Abstract

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.

Keywords

Treatment Development

Date concluded
12/31/2013

Treatment Type
Pharmacological: oxytocin

Target population
PTSD model Rats studies

IND
n/a

- Effects of oxytocin on methamphetamine-seeking exacerbated by predator odor pre-exposure in rats [55]

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Oxytocin Suppresses Alcohol Drinking and Relapse in Mice

Principal Investigator(s): Jacqueline F. McGinty, Ph.D. [3]
Medical University of South Carolina [4]

Lay Abstract

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.

Keywords

oxytocin, binge-like alcohol drinking, mouse models, relapse

Date concluded
8/31/2015

Treatment Type
Pharmacological: Oxytocin

Target population
Mouse Studies

IND
n/a

- Oxytocin Reduces Ethanol Self-Administration in Mice [56]
<table>
<thead>
<tr>
<th>Study/Product Aims</th>
<th>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>Keywords</td>
<td>PTSD, alcohol abuse, rat studies, lomerizine, Z160, N-type Calcium channel blockers</td>
</tr>
<tr>
<td>Date concluded</td>
<td>6/30/2013</td>
</tr>
<tr>
<td>Treatment Type</td>
<td>Pharmacological: Lomerizine &amp; Z160</td>
</tr>
<tr>
<td>Target population</td>
<td>Rat studies</td>
</tr>
<tr>
<td>IND</td>
<td>n/a</td>
</tr>
</tbody>
</table>

| Lay Abstract | 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). |
| Keywords      | treatment, pharmacotherapy, alcohol dependence, PTSD, zonisamide, cognitive processing therapy, alcohol use disorders |
| Date concluded | 6/30/2015 |
| Treatment Type | Pharmacologic and Cognitive Processing Therapy Combo: Zonisamide |
| Target population | Veterans with PTSD and AUD |
| IND            | exempt |
### Heat Shock Protein 90 at the Intersection of Alcohol Abuse and Stress: Preclinical Studies

**Principal Investigator(s):** Dorit Ron, Ph.D.  
**University of California, San Francisco**

| Lay Abstract | 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 |
| Keywords | alcohol abuse, alcohol relapse, HSP90 inhibitor, NVP-AUY922 |
| Date concluded | 6/30/2014 |
| Treatment Type | Pharmacologic: HSP90 inhibitor |
| Target population | Rat studies |
| IND | n/a |

### 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.  
**The Scripps Research Institute**

| Lay Abstract | 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. |
| Keywords | PTSD, relapse, corticotropin-releasing factor, kappa opioid receptor, alcoholism, ethanol reinforcement, dynorphin, self-administration behavior |
| Date concluded | 10/24/2014 |
| Treatment Type | Pharmacological: inhibition of the CRF-CRF1 or dynorphi-KOR stress systems (pexacerfont or CYM-50202) |
| Target population | Rat studies |
| IND | n/a |

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