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14. ABSTRACT

The goal of PASA is to fund research that aims to identify and develop new medications to improve treatment outcomes for alcohol use disorders (AUD) and substance use disorders (SUD), concurrently with post-traumatic disorders (PTSD) or other psychological disorders. Items for FY4 include:

- Launch of RFA6 and selection of 1 planning grant, 2 pre-clinical studies, and one non-clinical study for funding.
- Oversight and completion of three pre-clinical studies (AS170014-A1, AS170014-A2 and AS170014-A5)
- Launch of new pre-clinical ((AS170014-8) and non-clinical study (AAS170014-10)
- Systems development and launch of new clinical trial (AS170014-A7)

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1. Introduction

The Pharmacotherapies for Alcohol and Substance Use Disorder Alliance (PASA) is funded by the Congressionally Directed Medical Research Programs (CDMRP) as part of its Alcohol and Substance Use Disorder Research Program (ASUDRP). The goal of the PASA is to fund research for developing new medications that can improve treatment outcomes for alcohol and substance use disorders (ASUD), especially as related to post-traumatic stress disorder (PTSD) and other psychological disorders. Research proposed can be for an alcohol use disorder (AUD), substance use disorder (SUD), or both an AUD and SUD.

Clinical trials that include military service member and Veteran populations are highly desirable because these comorbidities are common in these populations. Alcohol use disorder (AUD) is the most common ASUD in the military, but opiate use disorder (OUD) also has developed significant clinical importance due to prolonged pain treatments with opiates. FDA approved pharmacotherapies are available for AUD, OUD, and PTSD. While TBI is of interest, it has no FDA approved specific pharmacotherapies, and none of these combined disorders have FDA approved pharmacotherapies. Under a Cooperative Agreement, RTI International is partnering with the CDMRP to solicit, select, and operationalize research studies that support the goals of PASA.

PASA has three aims under the primary objective to develop medications to treat ASUD in the context of the reciprocal relationship between ASUD, the physiological state of stress, and the subjective state of anxiety

- Aim 1: Discover: Test new chemical entities and repurpose existing medications in strictly pre-clinical and non-clinical models of ASUD with comorbid PTSD and other psychological disorders.

- Aim 2: Phase 1 First-in-Human Safety: Conduct clinical trials of potential medications that include assessment of medical safety and doses for potential efficacy in subjects with ASUD and comorbid PTSD and other psychological disorders.

- Aim 3: Phase 2 Efficacy: Conduct multiple site clinical trials to test preliminary efficacy and safety of potential medications or medication combinations in humans with ASUD and comorbid PTSD and other psychological disorders, and to also explore precision medicine tools for matching patients to these medications.

2. Keywords

- alcohol and substance use disorder (ASUD)
- alcohol use disorder (AUD)
- substance use disorder (SUD)
- opiate use disorder (OUD)
- post-traumatic stress disorder (PTSD)
- request for applications (RFA)
- pharmacotherapy

3. Accomplishments

In addition to monitoring and supporting ongoing studies, our primary objectives for the fourth year were:

- Issue request for applications (RFA#6) and get ready to launch studies in Year 5
- Launch the PT-150 study protocol
- Launch the Petrakis BXCL501 study protocol
- Launch the Lofexidine study protocol
- Implement the In-Silico proposal
- Implement Dr. Haile's Anti-Fentanyl Vaccine extension protocol
- Develop and publish primary manuscript for the pre-clinical testing of FKBP5 Inhibitors

3.0 PASA Activities

The PASA research program continued in year 4 with oversight of ongoing PASA work as well as the Research for Applications (RFA6).

3.0.a Primary objectives and milestones for the fourth year were:

A PASA objective is to efficiently manage and monitor studies that lead to accurate, quality data for publication and dissemination. This is achieved through PASA management responsibilities such as regularly scheduled check-ins, follow-ups, data accountability, statistical analysis, quality control and assurance, and other various oversight activities. Another objective of PASA is to ensure the PASA website remains a living entity with ongoing updates in order to ensure sites meet and maintain efficient feasible deadlines and milestones, as well as provide up to date, useful resources, and tools.

Consistent with the 3 Aims of this program as detailed in the Introduction, the overall focus of the PASA project is in (i) aiding in establishing priorities and endpoints for each project; (ii) providing scientific guidance in achieving project goals; and (iii) facilitating the navigation of challenges incurred in study conduct toward successful and timely completion of objectives. PASA ensured close communication with all research sites and tracked status through shared internal documentation.

At the start of year 4, PASA Leadership began developing the pre-clinical expansion for the Anti-Fentanyl Vaccine approved for funding at the end of year 3. This was awarded to support the continued research of a highly impactful study previously funded by PASA. During year 4, another request for research applications were released to the public to award pre-clinical, non-clinical, and planning grants/clinical studies under PASA. The Programmatic Panel funded 4 RFA submissions; two pre-clinical studies, 1 non-clinical study, and 1 clinical planning grant.

3.0.b Accomplishments under the goals include:

- Updated and maintained PASA website.
- RFA6:
    - Completed activities in support of RFA #6.
        - Released/distributed RFA

        - Received 58 Letters of Intent (LOI), resulting in 28 submissions, reviewed by Programmatic Panel with 1 planning grant, 2 pre-clinical studies, and one non-clinical project all approved for funding and implementation in FY 5.
- Studies/Projects:
    - Dr. Verrico's Lofexidine study began working on adding an additional site at the University of Texas Science Center at San Antonio.
    - Dr. Petrakis' BXCL501 study enrolled its first participants.
    - Sourced manufacturers for Dr. Haile's Anti-Fentanyl Vaccine.
    - Implemented the In-Silico non-clinical study.
        - The In-Silico study team submitted to the ASHG conference and was accepted for a poster presentation in the next quarter.
    - Developed and submitted 2 manuscripts for pre-clinical studies (Drs. Roberto and Haile), both which are pending publication.
    - Published 1 scientific article on the effects of PT-150 pharmacotherapy for opioid use disorder (OUD) and co-morbid post-traumatic stress disorder (PTSD) in the *Experimental and Clinical Psychopharmacology* journal.

3.0.c Training and professional development provided:
The PASA data coordinating center (DCC) staff performing study related activities on PASA are responsible for complying with training requirements set forth by RTI and federally mandated regulations. All PASA DCC staff performing study related activities train on the PASA and RTI standard operating procedures (SOPs). Exceptions to this requirement are for staff who solely manage either the PASA website or manage the financial/subcontracting processes. Individual staff are responsible for providing clearly labeled documentation of relevant training files for PASA.

For study site staff, PASA monitors that personnel are adequately trained on all relevant study documents, as warranted per their study role, including but not limited to the study protocol, manual of procedures (MOP), electronic data capture system (EDC), and other applicable study materials.

3.0.d Dissemination to communities of interest:
PASA currently hosts a public and private website. The private side of the website is password protected and can only be accessed by specified members of PASA and funded researchers. Study specific templates, tools, dashboards, and trackers are disseminated via the private side of the portal. The public side of the website allows dissemination of various public recourses and provides updates and opportunities related to PASA to general public.

PASA has also helped in dissemination of study data through collaboration on study specific manuscripts. PASA management personnel provide support in the development and finalization of all manuscripts.

3.0.e Plans for next reporting period to accomplish (goals and objectives):
Over the next reporting period, an ongoing focus will be providing support for our funded studies including launching the 4 new studies approved for funding from the RFA6 process. PASA plans to continue collaboration on presentations and manuscripts across all PASA studies.

3.1 AS170014-A1 Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy

The objective of this project is the development of an anti-fentanyl vaccine targeting fentanyl in combination with buprenorphine, a medication indicated to treat opioid use disorder (OUD). The conjugated antigen is constructed using CRM197 carrier protein and a hapten with fentanyl-like domains, and will be combined with dmLT, an adjuvant tested in humans with demonstrated safety and efficacy. The anti-fentanyl vaccine will be tested in rats alone, and in combination with buprenorphine to determine its antigenicity and ability to block the analgesic effects of fentanyl in rodent models. A successful adjuvant/vaccine formulation will be slated for cGMP manufacturing, toxicology, stability testing, IND-filing, and a Phase 1 clinical trial. Other experiments associated with this project involves testing buprenorphine in our animal model of Post-Traumatic-Stress Disorder (PTSD).

3.1.a Primary objectives and milestones for the fourth year were:

The major goals of this project were to investigate a novel combination therapy for the treatment of OUD and PTSD. The team's goals and objectives for this year were to complete the analyses of experiment data and compile them in a manuscript for peer review.

3.1.b Accomplishments under the goals include:

The major accomplishments under this goal was to re-assay and confirm anti-fentanyl (FEN) antibody levels in rats. As well as determine the contribution of antibody isotypes to measure the efficacy of the planned vaccine formulation funded separately from this award (AS170014-A8 for more information on vaccine progress).

3.1.c Training and professional development provided:

Nothing to report this period.

3.1.d Dissemination to communities of interest:

The study team delivered the presentation described below:

- *'Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-fentanyl Vaccine and Buprenorphine Combination Therapy, Colin N. Haile, Alcohol and Substance Use'; IPR 09/23/2021*
- Most recently, the study team submitted their primary manuscript form this work to the *Pharmaceutics* Journal.

3.1.e Plans for next reporting period to accomplish (goals and objectives):

Follow-up, as needed for publication of primary manuscript to a journal.

3.2 AS170014-A2 Pre-clinical assessment of PT150 for opioid use disorder and PTSD

Stressful events can serve as a potent trigger for relapse among individuals who are being treated for opioid use disorder (OUD), as well as serving as basis for inducing an anxiety disorder (PTSD) that can predispose an individual to OUD. The overall working hypothesis of this pre-clinical study is that selective blockade of glucocorticoid receptors (GRs) in the brain with PT150 will serve as an effective pharmacotherapy for OUD and co-morbid PTSD. In Aim 1, we

sought to determine if PT150 (0, 50 or 100 mg/kg, po) reduces stress-induced reinstatement of fentanyl seeking using a reinstatement model of relapse in rats. Stress was applied either environmentally (mild foot shock) or pharmacologically (yohimbine) and reinstatement of fentanyl seeking was measured. As presented in our last annual report, results from that experiment (Aim 1) showed efficacy for PT150 in reducing foot shock-induced fentanyl seeking, an effect that was primarily driven by males in the sample. In the current annual report, the team presents results from an experiment (Aim 2) which sought to determine if PT150 reduces fentanyl self-administration in individuals with co-morbid PTSD. Rats were exposed to two different models of stress: (1) chronic social isolation and (2) single prolonged stress (SPS) induced by restraint/swim, which have been used to model PTSD. When subsequently tested for fentanyl self-administration, isolated rats showed more intake of fentanyl than group housed rats and males self-administered more than females overall. PT150 negated the sex difference by decreasing intake in males, while increasing it in females.

3.2.a Primary objectives and milestones for the fourth year were:

The major accomplishments under this goal were to determine if PT150 reduces fentanyl self-administration in individuals with comorbid PTSD and develop a manuscript for submission to a scientific journal.

3.2.b Accomplishments under the goals include:

All major activities were accomplished under this goal including the following:

- All data collected and coded
- All data analyzed statistically
- Graphic representation of results completed
- First draft of manuscript was written, reviewed by co-authors and submitted for publication

3.2.c Training and professional development provided:

Dr. Cassie Chandler on the University of Kentucky team participated in the bi-weekly teleconferences with the staff of RTI. She was afforded the opportunity to gain insight into the workings of an independent non-profit institute that provides research, development, and technical services to academic, government and commercial entities worldwide.

3.2.d Dissemination to communities of interest:

The study team published in the Psychopharmacology Journal.

- *Hammerslag, L. R., Denehy, E. D., Carper, B., Nolen, T. L., Prendergast, M. A. and Bardo, M. T. (2021). Effects of the glucocorticoid receptor antagonist PT150 on stress-induced fentanyl seeking in male and female rats. Psychopharmacology (Berl). 2021;238(9):2439-2447. doi:10.1007/s00213-021-05865-0*

Dr. Bardo presented the study at the MOMRP meeting:

- *'Pre-clinical assessment of PT150 for opioid use disorder and PTSD Michael Bardo, Alcohol and Substance Use'; IPR 09/23/2021*

3.2.e Plans for next reporting period to accomplish (goals and objectives):

The study has concluded and does not have additional goals or objectives to complete.

3.3 AS170014-A5 Pre-clinical testing of FKBP5 Inhibitors for alcohol use disorder-PTSD comorbidity

Military personnel show high susceptibility to alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD). AUD is found among those with a military history more frequently than the general population (Hoerster, et al., 2012). AUD and PTSD display high comorbidity, as most veterans diagnosed with AUD have PTSD (Seal et al., 2010). Unfortunately, there is a lack of FDA approved pharmacotherapies for the treatment of PTSD/AUD comorbidity (Ralevski et al., 2014). Recently, the stress-related marker, FK506-binding protein 51 (FKBP5) might serve as a promising target in alleviating stress-related disorders (Pohlmann et al., 2017; Wang et al., 2018) and may assist in reducing AUD among patients with PTSD. This proposal examined the effects of FKBP5 inhibitors by using a highly specific FKBP5 inhibitor (SAFit2) or a more broad-acting, but FDA-approved FKBP5 inhibitor (benztropine) in a rodent model of PTSD/AUD comorbidity. The team hypothesized that FKBP5 inhibitors would reverse PTSD/AUD-like behaviors in our recently developed rat model of PTSD/AUD comorbidity (Steinman et al., 2020, in Molecular Psychiatry). This model increases voluntary alcohol intake and generates PTSD-like behavior responses in males and females in a manner relevant to the sexual dimorphism seen in human PTSD (Brown et al., 1995; Hourani et al., 2015), AUD (Zilberman et al., 2003), and comorbid PTSD/AUD (Lehavot et al., 2014; Sonne et al., 2003).

3.3.a Primary objectives and milestones for the fourth year were:

The major goals of this project were to investigate the effects of FKBP5 inhibitors on rats that displayed elevated PTSD/AUD-like comorbid behaviors. The team's goals and objectives for this year were to complete the behavioral analysis of Experiment 1A & 1B of the original grant project that involves administration of FKBP5 inhibitors, Benztropine and SAFit2. The study team was to analyze all the data and compile them in a manuscript for peer review.

3.3.b Accomplishments under the goals include:

Accomplishments include presenting at the MOMRP Alcohol and Substance Abuse IPR (2021) meeting and RSA Conference. The team finalized a manuscript and submitted it most recently to *Neuropsychopharmacology*. The study team also closed out regulatory approvals as needed.

3.3.c Training and professional development provided:

This project has provided extensive training and professional development opportunities. For the post-graduate fellows, Drs. Cruz and Vozella, this included compiling data for experiments, analyzing critical behavioral endpoints, and preparing and communicating the group's results for PASA meetings and manuscript writing.

3.3.d Dissemination to communities of interest:

Study data were uploaded to PASA web portal and the PASA management via a secure website. As mentioned, the study team presented at the MOMRP Alcohol and Substance Abuse IPR (2021) meeting. The team has also finalized their manuscript which has most recently been submitted to *Neuropsychopharmacology* and revised based on editorial comments. The study team also presented an abstract at the RSA Conference in June 2022.

3.3.e Plans for next reporting period to accomplish (goals and objectives):

As the study has concluded, the plan is to finalize publication efforts for the manuscript.

3.4 AS170014-A6 Lofexidine Combined with Buprenorphine for Reducing Symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans

The primary purpose of this Phase II, single center clinical trial is to evaluate the efficacy of Lucemyra™ (Lofexidine; LFX), an alpha-2-adrenergic receptor (α2-AR) agonist, as a medication for the prevention of opiate relapse and the alleviation of post-traumatic stress disorder (PTSD) symptoms in opiate-dependent veterans. The present trial was designed as an efficacy trial and utilizes a placebo-controlled, double-blind, single-site design. Currently, there is no non-opiate medication approved by the Food and Drug Administration (FDA) for this indication in the United States. If this trial demonstrates clinical safety and efficacy of LFX for opiate relapse prevention and/or PTSD symptoms, then the first clinical development accomplishment will be made paving the way for regulatory approval. Contingent upon the review and approval by the FDA, this will then permit the clinical development of LFX and depending upon the success of these other clinical trials may lead to a New Drug Application (NDA) for LFX for the indication of opiate relapse prevention and/or PTSD symptom alleviation. Therefore, the current trial has the potential of facilitating the regulatory approval of the first non-opiate medication for the prevention of opiate use relapse and/or alleviation of PTSD symptoms.

During the Screening Phase, potential participants will be reviewed for eligibility against inclusion and exclusion criteria, and eligible participants will be enrolled into the trial. Eligible participants will be randomized (1:1) to study agent (either LFX or PLB) using an adaptive randomization schema that will be implemented via an electronic data capture system. The dose of LFX will escalate over the first 3 study visits, at which point a flexible dosing regimen will be employed. Titration will occur in a blinded fashion such that individuals assigned to PLB will go through a similar perceived titration process as those in the LFX group. During the Treatment Phase, participants will receive medications and complete study procedures/assessments. During the Follow-Up Phase, participants will complete study procedures/assessments. The expected maximum duration of participation is up to 18 weeks, consisting of up to 30 days of screening, a 12-week treatment period, and a 2-week follow-up period. Notably, the goal is to determine whether there is enough evidence of efficacy and safety for this medication combination to support development of later phase clinical trials.

3.4.a Primary objectives and milestones for the fourth year were:

The overall objective of the proposed study is to determine if LFX as an adjunct to BUP treatment improves symptoms of both OUD and PTSD. The specific aims are two-fold: 1) To determine the proportion of veterans who achieve 30-days of sustained abstinence from illicit opioid use at the end of treatment with either PLB or LFX (up to 1.44mg/d) as adjuncts to BUP; and 2) To determine change from baseline scores on the PTSD Checklist (PCL-5) at the end of study. Our central hypothesis is that LFX as an adjunct to BUP treatment will reduce opioid use relapse and symptoms of PTSD in Veterans more effectively than treatment with BUP alone. Our specific hypotheses are: 1) compared to adjunct PLB, a greater proportion of veterans randomized (1:1) to adjunct LFX will submit opioid-negative urine drug screens (UDS) and self-report no opioid use across treatment weeks 5 to 12; and 2) veterans randomized to adjunct LFX will achieve a greater decrease on the PCL-5 at week 12. Our hypotheses are based on the distinct yet complementary mechanisms by which each medication reduces symptoms of both disorders.

Administrative goals for the year include the execution of a subcontract with UT Health Science Center at San Antonio, who will act as a second recruitment site. The research team is also working to hire and onboard new study personnel to act as alternatives for existing study personnel. The research group is working to reach the anticipated monthly recruitment goal of enrolling 8 PTSD and OUD veterans and non-veterans quarterly.

3.4.b Accomplishments under the goals include:
Administrative goals accomplished during the past year include receiving BCM IRB approval following the submission of multiple amendments, including:

- Expanding the inclusion criteria to allow comorbid conditions and modifying the compensation structure- approval granted on 12/01/2022
- Adding Ben Taub General Hospital as a recruitment site and opening recruitment to non-veterans- approval granted on 02/17/2022
- Updating the medications listed under to exclusion criteria at the request of the VA compliance Office- approval granted on 02/28/2022
- Modifications to how the study medication is prepared- approval granted on 6/13/2022

On 03/18/2022, the research team met with buprenorphine providers at Ben Taub to explore recruitment collaborative opportunities. In May 2022, Dr. Verrico presented about the Lofexidine study during MEDVAMC's Research Week, which included a participant testimonial from subject 01G010. Protocol approval for the 2022-2023 renewal period was granted on 08/18/2022. Fourteen (14) subjects have completed the preliminary screening visit since the last annual period. Of the 14 study subjects consented and enrolled, 12 have been randomized to the study conditions. Seven subjects have completed all study related visits since the last annual period.

3.4.c Training and professional development provided:
Baylor College of Medicine and the Michael E. DeBakey VA Medical Center regularly provides training courses for research personnel. Trainings seminars at Baylor College of Medicine are conducted by the Office of Research and Sponsored Programs Office and are Society of Clinical Research Associates (SOCRA) approved training programs.

3.4.d Dissemination to communities of interest:
The study is in active recruitment and data collection stage, with plans to disseminate information on hold until database lock.

3.4.e Plans for next reporting period to accomplish (goals and objectives):
A second recruitment site will be added to the protocol to increase recruitment. The research team is currently working to execute a sub-contract with UT Health Science Center, who will act as a second recruitment site for veterans suffering from PTSD and OUD. The study team also plans to hire additional research personnel to assist the recruitment and retention of study participants. The research team continues to collaborate with MEDVAMC and BTGH suboxone prescribers in efforts to increase recruitment rates. The research team plans to expand the number of suboxone providers currently listed as co- investigators.

3.5 AS170014-A7 Effect of Sublingual Formulation of Dexmedetomidine HCl (BXCL501) on Ethanol in Heavy Drinkers with PTSD- Alcohol Interaction Study

The overall objective of the proposed study is to determine if Dexmedetomidine HCl (BXCL501) is safe for treatment of alcohol use disorder (AUD) with comorbid posttraumatic stress disorder (PTSD) and also shows potential signals of efficacy thereby supporting the conduct of later phase clinical trials. Safety endpoints will be compared following an alcohol challenge without and concurrent with BXCL501 treatment.

This laboratory study is a phase 1, double-blind, placebo-controlled, within subjects' study. This study will consist of 3 laboratory test sessions following pretreatment with BXCL501/placebo for 10 heavy drinker participants with comorbid PTSD. Study participants will participate in a laboratory study with 3 test days (minimum of 2 days, but no longer than 2 weeks between each test day). Each test day the participant will be assigned to receive sublingual BXCL501 40µg, 80µg and placebo in a randomized fashion. Test days will be conducted to evaluate stress (PTSD) reactivity and alcohol cue reactivity. Participants will also receive IV ethanol administered via "clamp methodology" to assess for the effects of BXCL501 in combination with ethanol.

3.5a Primary objectives and milestones for the fourth year were:

The overall objectives for the fourth year were to obtain Office of Human Research Oversight (OHRO) approval, finalize the study's budget, develop plan for recruiting subjects and start recruiting for study 1.

3.5.b Accomplishments under the goals include:

In September 2021, the study team trained a new research assistant, finalized forms, received ethanol, and finalized the MOP. In October 2021, the COVID guideline was approved, training was scheduled and signed-off on. In November 2021, the study site began recruitment. The study team used various recruitment methods including posting flyers and sending letters to potential participants. Additionally, the study team work on the IND annual report. In December 2021, the study team created a billboard advertisement and a brochure to hand out in hopes of increasing recruitment efforts. By January 2022, the billboard was launched and the team began working with Trialfacts to support recruitment efforts. Additionally, the study team completed the continuing review for the VA IRB. In February 2022, the study team amended the protocol to increase the age range from 50 to 65. The amendment submission also included new advertisement methods such as craigslist and Trialfacts. February-April 2022, the team continued efforts to increase recruitment and screenings. March 2022, Trialfacts and other recruitment efforts were approved. The protocol for the age increase was approved. In May 2022, the study team submitted a protocol amendment to change the PTSD criteria and increase payment for study. Recruitment started from Trialfacts. In June and July, 3 participants were enrolled and randomized into the study. The MOP was revised and Dr. Louis Trevisan was a medical back up for Dr. Petrakis was added. In August 2022, 1 more subject was randomized. The MOP was finalized. In September 2022, study team began to consider drafting study materials for study 2 (with the understanding that study 1 results need to be done and FDA-reviewed before Study 2 gets considered for implementation). Recruitment efforts were continued.

3.5.c Training and professional development provided:
Site study staff have all been trained and signed-off on study specific trainings.

3.5d Dissemination to communities of interest:
Currently the study is actively recruiting participants, with the hopes that this project may produce a medication to potentially treat comorbid PTSD and AUD.

3.5.e Plans for next reporting period to accomplish (goals and objectives):
Once the study team enrolled and completes study activities for all subjects in Study 1, a protocol for Study 2 will be finalized based on findings from Study 1. The study team will send the protocol for Study 2 and safety data to the FDA and appropriate regulatory entities, for their consideration for approval to move forward with Study 2.

3.6 AS170014-A8 Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy
Illicit synthetic opioid use has led to increases in opioid use disorder (OUD) and accidental opioid-related overdose deaths creating a significant public health crisis. Over a period of 12 months, (2019-2020) overdose deaths in the United States increased to the highest ever recorded (81,000) and alarmingly, the latest statistics are even higher with nearly 70% of all overdose deaths (96,700) involving opioids. Also concerning is that overdose deaths have dramatically increased in young people (age 10-24 years). Most recent estimates indicate the years of life lost secondary to unintentional drug overdose over a 5-year period (2015-2019) is greater than 1.25 million years. Fentanyl (FEN) is a highly potent μ opioid receptor agonist indicated for the treatment of moderate to severe pain. FEN and FEN-analogs (e.g., carfentanil, sufentanil, alfentanil, lofentanil) are highly lipophilic and rapidly penetrate the CNS which can be lethal. The standard medication to reverse FEN's effects is the mu antagonist naloxone. Because of FEN's potency however, high doses of naloxone are needed in a timely manner to avert overdose. A novel alternative treatment strategy to avoid overdose and prevent relapse in individuals with OUD is by vaccination with an anti-FEN vaccine.

The study team's primary goal in PASA2 was to develop an anti-FEN vaccine to address the opioid epidemic. Overall, the study team completed the primary goals of these PASA2 studies: 1) the team generated an anti-FEN vaccine, 2) showed that vaccinated animals produced appreciable anti-FEN antibody levels, 3) demonstrated near complete blockade of FEN's analgesic effects in vaccinated animals, 4) discovered promising interactions of buprenorphine with the vaccine and, 5) determined that the vaccine prevented FEN from entering the brain in both male and female rats. The expansion studies are allowing the study team to determine whether our anti-FEN vaccine will attenuate FEN's reinforcing effects and importantly, assess whether it will block FEN-induced effects on physiology, such as hypoxia and bradycardia linked to drug overdose and death. Other support is for the manufacture of clinical grade vaccine for toxicology studies and eventual FDA approval for a Phase 1 clinical trial.

3.6.a Primary objectives and milestones for the fourth year were:
There were three aims for the fourth year which are the following:

AIM1. *Rats vaccinated with FEN-CRM+dmLT will generate significant anti-FEN antibodies that will block FEN-induced reinstatement of drug-seeking behavior.*

AIM2. *Rats vaccinated with FEN-CRM+dmLT will generate significant anti-FEN antibodies that will block FEN-induced decreases in heart rate, respiratory rate and oxygen saturation and thus increase survival following a high dose of FEN.*

AIM3. *The study team will contract to manufacture clinical grade (cGMP) components of the vaccine for conjugation under appropriate subcontracts.*

3.6.b Accomplishments under the goals include:

Aim 1. First, the study team replicated and further characterized the efficacy of their vaccine to generate anti-FEN antibodies and determined whether these antibodies cross-react with other FEN-derivatives. Ongoing studies include assessing the ability of the vaccine to block drug-induced reinstatement of drug seeking behavior in an animal model of relapse.
Aim 2. During this period of performance, the study team has completed the overdose study and definitively show that their FEN-CRM vaccine in combination with the adjuvant dmLT blocks FEN's effects on multiple physiological measures in both male and female rats. The study team also discovered that FEN has greater effects on the physiology of male rats compared to female rats.
Aim 3. The study team has established contractual relationships with Vici Health Sciences (Elkridge, MD) to synthesize clinical grade hapten and the Walter Reed Army Institute of Research (WRAIR) (Silver Spring, MD) to synthesize the conjugate vaccine.

The following activities were completed during this period of performance:

- Cross-reactivity study
- FEN-induced overdose study
- Contract with Vici Health Sciences to produce GMP-grade hapten was finalized
- Contract with Walter Reed Army Institute of Research to perform the conjunction was finalized.

Methods are described below:
Antigens and adjuvants
FEN-BSA, morphine-BSA, methadone-BSA, buprenorphine-BSA and oxycodone-BSA were purchased from Cal BioReagents. FEN-CRM was synthesized using a FEN derivative with a carboxylic acid linker coupled to lysine residues on CRM197 (Fina Biosolutions). The FEN hapten was created in a series of four chemical reactions. The product of each step was characterized and validated by 1H and 13C NMR spectrum and purity of the FEN hapten was validated by HPLC. The final product was then conjugated to CRM197 as described in detail [26]. Prior to immunization, the conjugate was dialyzed in PBS (Slide-A-Lyzer, Thermo Scien-tific), sterilized by passing it through a 0.2um filter (Acrodisk, Life Sciences) and quantified using a protein assay kit (BCA, Pierce). GLP–grade dmLT was produced according to cyclic GMP (cGMP) specification by IDT in sodium phosphate buffer supplemented with 5% lactose in vials containing 400-µg of lyophilized product in a 3-mL sterile, multidose, Wheaton serum vial and stored at 4°C. dmLT was re-suspended prior to use with IXPBS.

Immunization and Sample Collection
The vaccine formulation (5µg FEN-CRM + 1µg dmLT) was prepared immediately before administration by admixing antigen and adjuvant in sterile PBS in a 100-µL volume per vaccination per animal. Animals were injected with a 0.5cc insulin syringe into the right and left

caudal thigh muscle (50-µL per hind limb) Immunizations occurred at 0, 3 and 6 weeks. Blood samples were collected from the saphenous vein on weeks 4, 6, 8 and 10 post-initial vaccination. Following administration of the high dose of FEN (0.1 mg/kg) a final collection occurred at week 20 whereby rats were placed under isoflurane anesthesia and the heart exposed via bilateral thoracotomy and blood obtained by cardiac venipuncture. The brain was also removed at this time.

Antibody Levels, Cross-reactivity and Fentanyl Quantification

Anti-FEN antibodies were quantified by using corning 96 well flat bottom plates (Costar 9018) that were coated with 0.2-µg FEN-BSA and detected using AKP-conjugated anti-rat IgG (Sigma). ELISAs were quantified using dilutions of purified rat standard IgG (Sigma) to generate a standard curve that were used to calculate IgG anti-FEN antibody concentrations in samples. Results are ex-pressed as ELISA units/ml. Potential cross-reactivity to various antigens other than FEN-BSA was assessed using the same ELISA methods with the exception that the plate was coated with morphine-BSA, methadone-BSA, buprenorphine-BSA and oxycodone-BSA and serum samples from unvaccinated and vaccinated rats assayed. Concentrations of anti-FEN antibodies for both assays were quantified using four-parameter logistics curve fitting from symmetrical sigmoidal calibrators.

Physiological effects: Overdose study

A non-invasive pulse oximetry system (Mouse004F Plus, Starr Life Sciences, Oakmont, PA) was used to measure the ability of our conjugate vaccine to attenuate FEN-induced depression on oxygen saturation, heart rate, and general activity in both male and female rats. Rats were first acclimatized to the sensor that was placed around the dorsal neck for two consecutive days in the testing room. Rats were then habituated to the testing chamber (Coulbourn Instruments, Holliston, MA) for 30-m with the sensor attached to the rat and baseline measures recorded. Following habituation, rats were administered FEN (0.1 mg/kg, SC) and placed back into the testing chamber and measures recorded for 30min. The study team chose this time point based on preliminary studies showing near recovery from FEN-induced decreases on oxygen saturation post-FEN administration in both male and female rats.

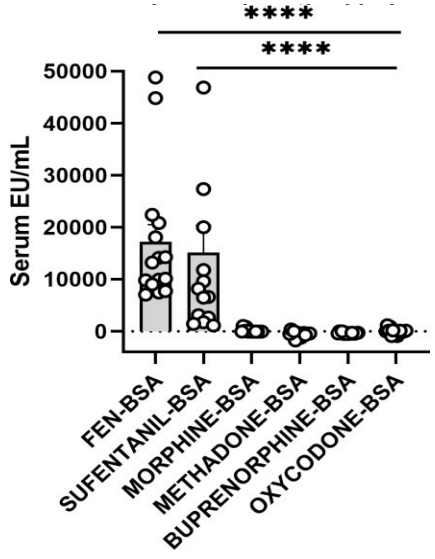


Figure 1 displays ELISA cross-reactivity assay results.

Cross-Reactivity Assay

ELISA cross-reactivity assay results are presented in **Figure 1.** Serum from vaccinated male rats collected at 20 weeks post initial vaccination was assayed. Analysis of anti-FEN antibody binding to various opioid haptens yielded a highly significant main effect for vaccine status ($F(1, 167)=26.33$, $P<0.0001$), coating antigen ($F(5, 167)=11.27$, $P<0.0001$), and a significant interaction ($F(5, 167)=11.52$, $P<0.0001$). Post hoc analysis revealed significant differences between FEN-BSA and all other coating antigens (****P's<0.0001).

Physiological Effects: Overdose Study

The effects of high dose FEN on oxygen saturation, heart rate, and activity levels in male and female rats are presented in **Figure 2A-F**. Analysis of oxygen saturation data revealed significant main effects for Sex ($F(1, 25)=5.33$, $P<0.05$), Vaccine status ($F(1, 25)=59.87$, $P<0.0001$), Time ($F(6,150)=19.52$, $P<0.0001$), and significant interactions of Sex X Vaccine status, ($F(1,25)=6.05$, $P<0.05$) and Time X Vaccine status ($F(6, 150)=16.62$, $P<0.0001$). Post-hoc comparisons revealed significant differences between male vaccine groups at 5-m ($P<0.05$), between vaccine groups of both sexes at 10-, 15-, and 20-m, (P's<0.01-0.0001), and between male vaccine groups at 25-m (P's<0.01-0.001). FEN decreased oxygen saturation in both male and female unvaccinated rats that was blocked by the vaccine. Analysis of heart rate (bpm) revealed significant main effects for Sex ($F(1, 25)=23.06$, $P<0.001$), Vaccine status ($F(1, 25)=26.74$, $P<0.001$), Time ($F(6, 150)=13.72$, $P<0.0001$), and a significant Time X Vaccine status interaction ($F(6, 150)=6.24$, $P<0.0001$). Post-hoc analysis revealed a significant difference between male vaccine groups at 10-m (P's<0.01), indicating that the vaccine blocked FEN-induced decrease in heart rate. Analysis of activity counts revealed significant main effects for Sex ($F(1, 25)=113.42$, $P<0.0001$), Vaccine status ($F(1, 25)=36.37$, $P<0.0001$), and Time ($F(6, 150)=6.96$, $P<0.0001$) and significant Sex X Vaccine status ($F(1, 25)=7.55$, $P<0.05$) and Time X Vaccine status ($F(6, 150)=5.43$, $P<0.0001$) interactions. Post-hoc comparisons revealed significant differences between male vaccine groups at 20- and 25-m (P's <0.01). FEN significantly decreased activity counts in male rats and the vaccine blocked this effect. FEN-induced decreases in activity counts were significantly lower in male rats compared to female rats.

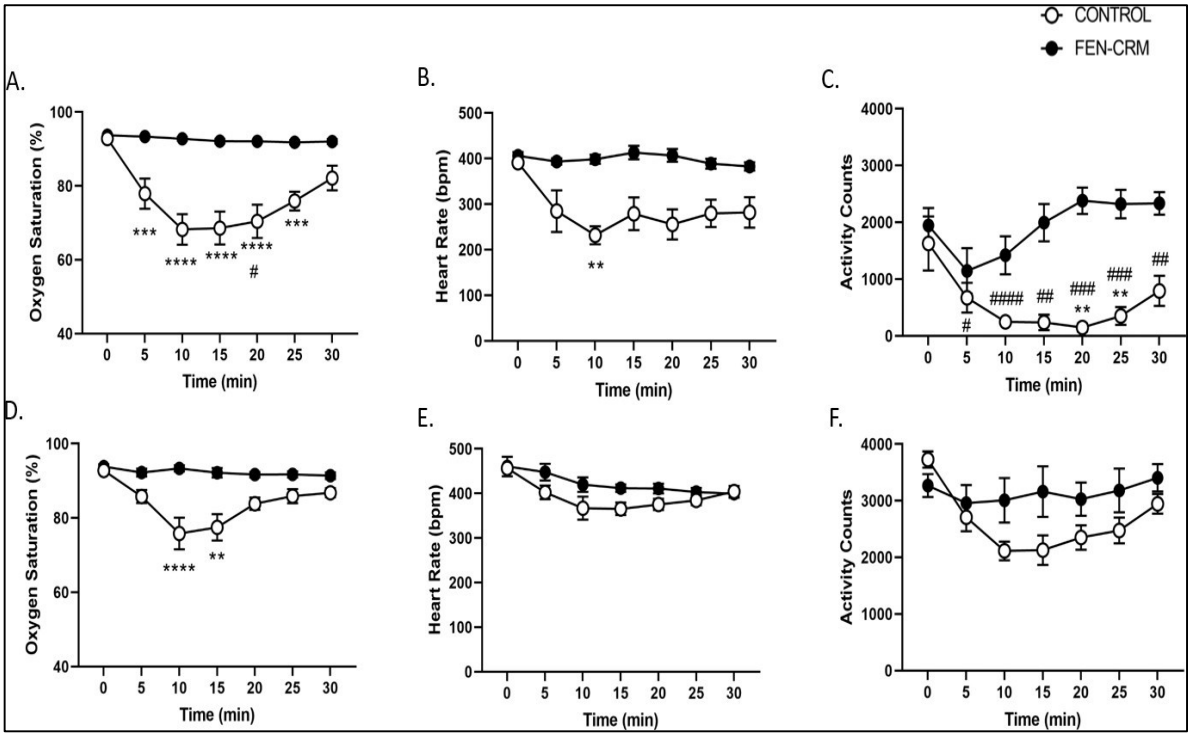


Figure 2 displays vaccine efficacy against FEN-induced physiological effects in male and female Sprague Dawley rats. Sprague Dawley rats (male, CONTROL, N=6, FEN-CRM, N=8, A.-C.; female, CONTROL, N=9, FEN- CRM, N=6, D.-

*E.). Groups were vaccinated with PBS or FEN-CRM+dmLT (day 0, 3 and 6 weeks, IM) and at approximately 10 weeks post initial vaccination rats were administered 0.1 mg/kg FEN (SC) and oxygen saturation (%), heart rate (beats per minute, bpm), and activity (counts) were measured using a pulse oximetry system. FEN significantly decreased all measures in unvaccinated male rats and these effects were attenuated by the vaccine. FEN significantly decreased oxygen saturation in unvaccinated female rats that was reversed by vaccination. CONTROL vs. FEN-CRM male and female groups: ** P<0.01, *** P<0.001,**** P<0.0001; CONTROL male vs. CONTROL female groups: #P<0.05, ## P<0.01, ### P<0.001, ####P<0.0001.*

Conclusions are detailed below:

- Anti-FEN antibodies generated from our vaccine cross-react with FEN-derivatives like sufentanil but no other opioids such as morphine, methadone, buprenorphine or oxycodone.
- It is well known that illicit FEN is contaminated with numerous FEN derivatives and that our vaccine may provide protection against these lethal compounds.
- Our anti-FEN vaccine blocks high-dose FEN-induced decreases in oxygen saturation (hypoxia), decreases in heart rate (bradycardia) and general activity and the magnitude of this effect was greater in male rats compared to female rats.
- The study team observed a significant sex effect in that high-dose FEN decreased all measures in unvaccinated male rats whereas only oxygen saturation was significantly, although briefly, decreased in female rats.

3.6.c Training and professional development provided:
Nothing to report for this period.

3.6.d Dissemination to communities of interest:
Journal articles:

- One published manuscript,
- One manuscript under review, and
- Another being generated for submission.

3.6.e Plans for next reporting period to accomplish (goals and objectives):
The study team plans to complete the self-administration study, submit a third manuscript characterizing the anti-fentanyl vaccine, and manufacture a clinical grade vaccine for toxicology studies and a phase 1 clinical trial.

3.7 AS170014-A10 Leveraging multi-omic data integration for in silico compound prioritization

This project seeks to leverage large-scale robust evidence across omic domains to produce a catalog of biological targets and candidate compounds for future drug repurposing studies aimed at improving the effectiveness and trajectory of treatment for alcohol and substance use disorders (ASUDs) and/or posttraumatic stress disorder (PTSD). This catalog will be made possible by collecting existing multi-omic results, performing integrated analyses, and systematically searching target-compound databases. The catalog will include summaries of the supporting evidence for the target or compound's inclusion and ranking. This actionable, interpretable, and annotated resource will be made available to the drug repurposing community who are the intended recipients of PASA-funded pre-clinical and clinical trials. The results will also provide an unbiased distillation of evidence across multiple domains which will

aid in the evaluation of future proposals received by PASA. To produce such a resource, the project has three aims including: 1) Identifying genetic loci influencing common versus specific risk to PTSD, AUD, and OUD 2) Identifying gene expression modules enriched for ASUD and PTSD liability, and) Prioritizing therapeutic compounds targeting risk genes and modules.

3.7.a Primary objectives and milestones for the fourth year were:

Aim 1: *Identify genetic loci influencing common versus specific risk to PTSD, AUD, and OUD:*

1a) Collect genome-wide association studies (GWAS) meta-analyses of ASUDs, PTSD, and comorbid psychiatric disorders.

1b) Leverage cross-disorder genetic correlations to disentangle pleiotropy to identify gene targets common and specific to PTSD, AUD, and OUD risk.

Aim 2: *Identify gene expression modules enriched for ASUD and PTSD liability:*

2a) Collect gene expression studies of post-mortem human brains.

2b) Perform cross-omic network analysis to detect expression sub-modules enriched for genes both common and specific for influencing risk to PTSD, AUD, and OUD.

Aim 3: *Identify and prioritize therapeutic compounds:*

3a) Rank all genes in human genome using the combined evidence from a) individual risk loci (Aim 1) and b) network analysis (Aim 2).

3b) Identify compounds targeting high ranked genes and networks by searching multiple compound identification and drug repurposing resources.

3c) Produce a catalog of genes and compounds to inform repurposing studies of ASUD and PTSD.

3.7.b Accomplishments under the goals include:

Aim 1

- Completed an in-depth review of genome-wide association studies (GWAS) summary statistics available for opiates, alcohol, and post-traumatic stress disorder (PTSD) related phenotypes. A major focus of this review was assessing independence or potential overlap in samples across studies since independent samples are preferred for network analyses in Aim 2.
- Selected opiate related GWAS for phase 1 full analysis pipeline. Transferred data and documentation to common project analysis / computing resource.
- Prepared applications to gain access to newly identified GWAS results for gSEM analysis and gene-ranking (Aim 3).
- Participated and collaborated with the Psychiatric Genomics Consortium (PGC) PTSD working group and the VCU PTSD genetics team to keep up to date on the latest advances in PTSD genetic studies. The PGC PTSD group recently completed but yet unpublished GWAS represents the largest genetic study of PTSD to date. This collaboration will facilitate pre-publication access to these results. The VCU PTSD team has performed preliminary gSEM analyses which are complementary to this project's aims. Leveraging the VCU group's experience will making our own analyses more efficient.

- Planning for gSEM analyses across diverse ancestries. To date, almost all gSEM based analyses are limited to samples with subjects of European ancestry. As part of another project, project investigators are developing an African American linkage disequilibrium (LD) score reference. The reference will facilitate gSEM analysis in samples with African American ancestry such as the PGC and Millions Veteran Program (MVP) GWASs of PTSD.
- Prepared dbGaP application for the Million Veterans Program (MVP) GWAS summary statistics, including analyses of alcohol, opioid, and PTSD related phenotypes.
- Adapted and tested R script pipeline to run GWAS-by-subtraction using the GenomicSEM R package. This reproducible pipeline will be used in Phase 2 to identify genetic loci common and specific to AUD, OUD, and PTSD.

Aim 2

- Trained team members in network analysis methods dmGWAS (Quach, Willis) and WGCNA (Willis).
- Investigated feasibility of restricting Protein-Protein Interaction (PPI) networks to those a) specific to humans, b) present in brain, and c) with experimental evidence.
- Performed network analyses via dmGWAS on opioid use disorder (OUD) GWAS data using summary statistics from GENOA and MVP12 studies using both a) default PPI networks and b) PPI network present in human brain.
- Evaluated the impact of using tissue specific (brain only) protein-protein interaction networks on dmGWAS gene module search space and resulting network enrichment results.
- Obtained human prefrontal cortex gene expression data from four different OUD related datasets. These were then (re)processed through an internally developed, automated RNA sequencing data processing workflow to minimize cross study heterogeneity. These data also have corresponding published summary statistics for differential gene expression analysis by opioid use status that will be combined with the dmGWAS output to be used as ranking variables for Aim 3.
- Performed meta-analysis of gene expression from human prefrontal cortex associated with OUD status. This approach enables us to aggregate differential expression p-values from each study into a single p-value to simplify the ranking system for Aim 3.
- Constructed gene co-expression networks using WGCNA as non-PPI based inputs for dmGWAS network analyses. The goal is a unified modeling framework for more gene network-centric dmGWAS output for use in gene rankings for Aim 3.
- Due to computational bottlenecks with using the official source code for ew-dmGWAS, the software has been partially refactored to address these bottlenecks. Benchmarking of the network size impact (i.e., number of nodes) on runtimes for gene-gene interaction network construction and parameter selection were conducted.
- Began modifications to ew-dmGWAS to incorporate gene co-expression networks from the opioid's gene expression datasets.

Aim 3

- Investigated drug repurposing databases and resources including Open Targets, Pharos, CMAP, Drug Gene Budger, Genome for Repositioning drugs, and Drug Targetor. Evaluated which information in these resources would be useful in ranking of gene targets.

- Tested API and other query tools to determine the best mechanism for dynamic querying of Open Targets, a drug development and repurposing database and resource. Reviewed API EndPoints with the team and selected the most essential variables for drug repurposing weighting. Developed scripts to pull these data from Open Targets.
- Completed a R-script for large-scale querying of OpenTargets database via its API.
- Adapted OpenTargets script to pull data directly from Pharos database. All Tclin and Tchem target-ligand associations were downloaded to be used for the Aim 3 prioritization.
- Performed data integration of selected information from Pharos with opiate related gene-wise MAGMA association results (from Aim 1).
- Extracted and merged information on druggable gene targets from Open Targets, Pharos, DrugBank, and Therapeutic Target Database into an integrated summary.
- Develop a pilot pipeline / algorithm to a) integrate extracted information from multiple drug repurposing databases, b) weight different features including approval status, target selectivity, target affinity, toxicity and safety, and c) generate a ranked score for each gene target.

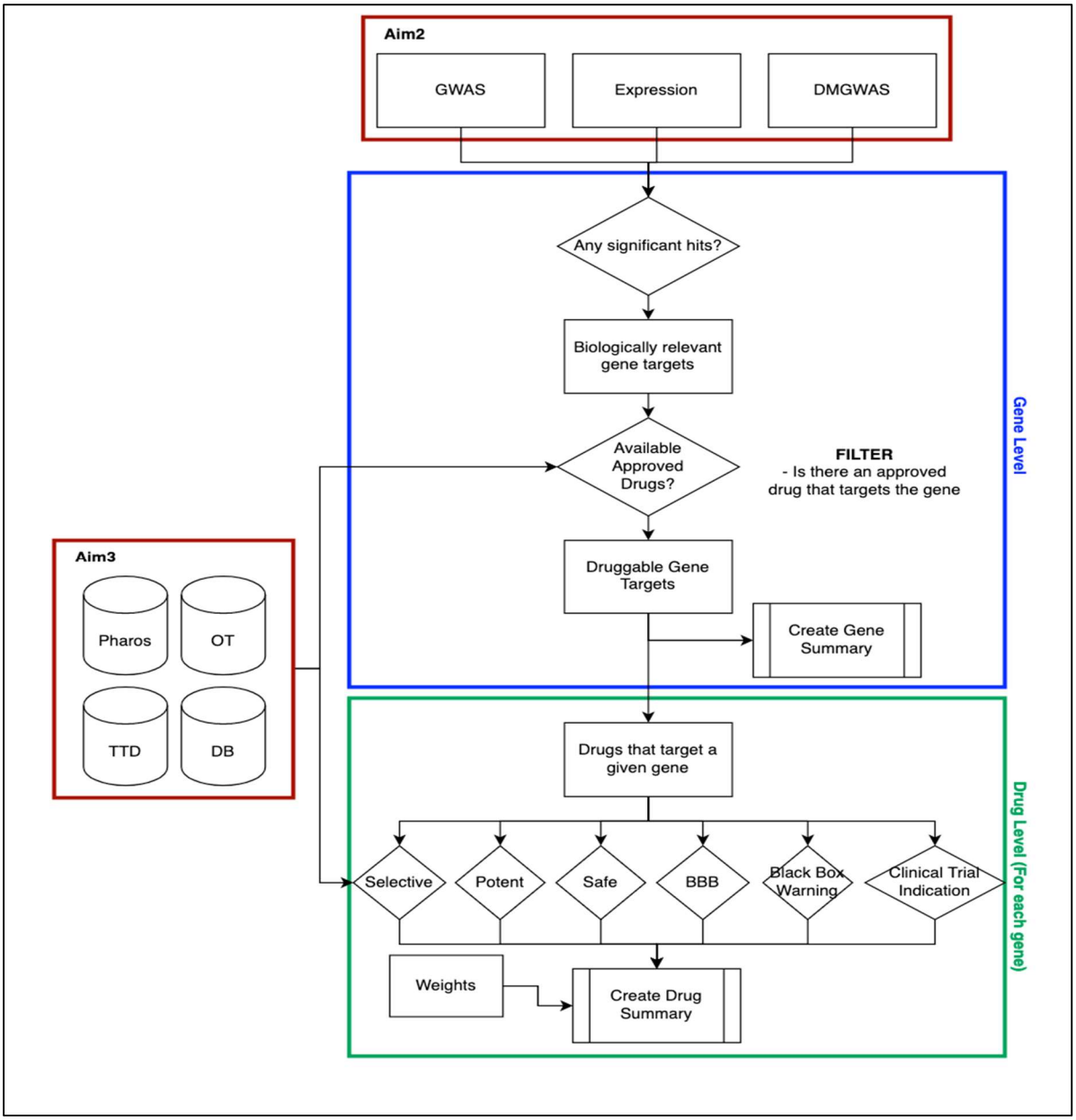


Figure 3 displays the schema of pilot data integration and compound identification pipeline.

- Developed prototype dashboard for gene & drug prioritization with the following features
  - Allows users to select biological evidence to include in the prioritization ranking.
  - Integrate multiple sources of biological evidence including network analyses.
  - Filter available compounds for repositioning based on user supplied inputs about database source, approval/clinical status, and drug characteristics.
  - Produce a list of compounds that target a specific gene target.

3.7.c Training and professional development provided:

No formal training or professional development activities were included in the scope of work. However, various members of the analysis team gained new or deeper experience in analytic domains used in the project. For example, Bryan Quach and Caryn Willis gained experience in

network analyses by applying dmGWAS and WGCNA under the direction of the PI. For professional development, Jeran Stratford will present a poster at the annual meeting of the American Society of Human Genetics which will help to raise his scientific stature which is an important component of career development.

3.7.d Dissemination to communities of interest:
Interim results were presented internally to other members of omics research community at RTI, both formally and informally. A summary of the first phase of the project was submitted and accepted for a poster presentation at the annual meeting of the American Society of Human Genetics

3.7.e Plans for next reporting period to accomplish (goals and objectives):
The study team plans to refine the existing pilot pipeline. The primary shift will be to focus on cross-disorder data integration. In the first year, the study team limited analyses to opiate related data. The next phase will include opiate, alcohol, and PTSD related datasets.

4. Impact

4.0 PASA Management
Results Dissemination:

The work, findings, and specific products of the projects sponsored through PASA are ongoing, but collaboration on manuscripts and presentations has provided quality data to push innovations forward. As the PASA DCC and study leaders continue to finalize and publish additional manuscripts, this strengthens PASA's impact.

Pharmaceutical Partners:

Another important impact during this reporting period has been with our pharmaceutical company partners. These partners have favorably noted our major accomplishments, innovations, and successes for identifying promising new medications for substance use disorders.

Future Projects:

PASA has refined the RFA and project award process to better identify viable projects and to make initial low-funded awards to allow for better determination of clinical trial needs for potential compounds.

Leveraging PASA Output:

PASA continues to build our template library as well as the PASA website to allow for efficiency and consistency across studies. PASA has also established excellent working relationships with several VAMCs across the USA for conducting our PASA clinical studies. PASA has used knowledge across studies conducted within the PASA, as well as knowledge of clinical trials conducted outside of the PASA with the PASA established collaborators, to help inform initial and continued funding decisions for compounds being studied within PASA. To further expand on our ability to select novel compounds efficiently and effectively, PASA has recently funded an In-silico project. This work will help to generate a formalized catalog of promising compounds that can then be incorporated into clinical or pre-clinical pursuits based on their novelty and fit in the regulatory pathway. Taking this additional step before

implementing trials will help identify innovative therapies, ensure resources are utilized efficiently, and achieve the goal of expediting the translation from bench to bedside.

4.1 AS170014-A1 Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy

The team has made significant progress in the development of the anti-fentanyl vaccine during the reporting period to the extent in which the plans include to manufacture of clinical grade vaccine for toxicology testing and a Phase 1 clinical trial. With this progress and as mentioned above, the University of Houston intellectual property committee continues to support and execute the study's provisional patent to full patent status [*Colin N. Haile, Gregory D. Cuny, Elizabeth B. Norton, Therese A. Kosten, Adjuvanted Conjugate Opioid Vaccine (05/27/2020)].*

4.2 AS170014-A2 Pre-clinical assessment of PT150 for opioid use disorder and PTSD

The results of this pre-clinical project provide the initial proof-of-principle evidence that PT150 has differential effects in males and females in ameliorating stress-induced escalation of fentanyl self-administration, thus providing the impetus for a potential new avenue for treating co-morbid OUD and PTSD, at least in males. Further work is needed to determine the mechanism(s) underlying the differential effect of PT150 in males and females, which will be critical for potential translation to humans.

4.3 AS170014-A5 Pre-clinical testing of FKBP5 Inhibitors for alcohol use disorder-PTSD comorbidity

The study team successfully used for the first time a novel PTSD/AUD comorbidity model recently developed and characterized in our laboratory (*Steinman et al., 2020, in Molecular Psychiatry*). The model has shown efficacy in generating non-associative fear sensitization as well as Pavlovian and operant conditioning and has more translational value for PTSD and drinking behavior. Using this comorbidity model, the team was able to identify effects of benztropine, an FDA-approved drug, and SAFit2, a selective FKBP5 inhibitor, to significantly reduce voluntary ethanol drinking and, in females, acoustic startle responses, a putative indicator of hyperarousal (Benztropine only). This work is informative and will hopefully soon be accepted for publication and useful for identifying future studies to potentially pursue.

4.4 AS170014-A6 Lofexidine Combined with Buprenorphine for Reducing Symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans

This project is in early stages of recruitment; however, the site anticipates a positive impact in the near future. The team is dedicated to enrolling participants and collecting data accurately and efficiently to ensure the study is scientifically significant in studying symptoms of PTSD and opioid use relapse.

4.5 AS170014-A7 Effect of Sublingual Formulation of Dexmedetomidine HCl (BXCL501) on Ethanol in Heavy Drinkers with PTSD- Alcohol Interaction Study

This project is still actively recruiting; however, the site anticipates a positive impact in the near future. The team is dedicated to enrolling participants and collecting data accurately and efficiently to ensure the study is scientifically significant in studying symptoms of PTSD and opioid use disorder.

4.6 AS170014-A8 Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy

The development of a potential treatment to address OUD and opioid overdose is of extreme importance since deaths from fentanyl and other synthetic opioids is continuing to rise. The study team has made significant progress in the development of our anti-fentanyl vaccine during the reporting period to the extent in which our plans include the manufacture of clinical grade vaccine for toxicology testing and for a Phase 1 clinical trial.

4.7 AS170014-A10 Leveraging multi-omic data integration for in silico compound prioritization

A meaningful finding resulting from this project is that the use a single drug repurposing database is not sufficient to identified all promising compounds. While we expected this to be the case, this can now be demonstrated empirically. While drug repurposing databases are widely available to scientists working to discover genes influencing risk (GWAS) or measuring the neurobiological signatures (expression) related to a disorder, the ability to look up and summarize the compounds targeting large numbers of genes was not practicable for most researchers. The results of this project will facilitate the rapid look up of many targets. This has potential utility beyond the target disorders (AUD, OUD, PTSD).

5. Changes/Problems

5.0 PASA Management

The main challenge in the past year has been impact of the COVID-19 pandemic on research. Overall, most of the pre-clinical studies did not experience significant setbacks; however, there were some study delays and modifications to some pre-clinical study and clinical trial protocols/procedures due to the pandemic. To mitigate study barriers as much as possible, PASA tracked each site's status and routinely assessed for impacted abilities at the site level. Though there were some delays, sites are now fully reopened and operational and have adapted to the constraints brought about by COVID. Of important note is that regulatory approvals from FDA and DoD advisory boards, as well as local IRB and VA R&D committees, remain on track for successful resolution of projects since COVID-19 restrictions were lifted.

5.1 AS170014-A1 Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy

The study team has completed all required activities in this study, publication of manuscript is completed.

5.2 AS170014-A2 Pre-clinical assessment of PT150 for opioid use disorder and PTSD

Due to the shutdown of the University of Kentucky in March 2020 in response to the COVID-19 pandemic, project completion was delayed (with project extension granted). COVID-19 delays have also increased some project line-item expense; with supplemental funding resolving that issue.

5.3 AS170014-A5 Pre-clinical testing of FKBP5 Inhibitors for alcohol use disorder-PTSD comorbidity

The study team had extinguished the PASA funds as of November 2021. Due to pandemic (COVID-19) restrictions, personnel conducting the proposed studies were working at a limited capacity due to institutional constraints on personnel density as well as vivarium housing density constraints. This protracted the duration of the project, and extended personnel cost (originally budgeted for a shorter time). After discussions with PASA leadership, focus was geared towards having proper controls for

studies involving Aim 1. Additionally, as a result of the cost of running additional controls for the SAFit2 studies and the pandemic constraints of reduced animal and personnel density extending project duration, funds were exhausted to perform Aim 2 regarding the chronic studies. The study team continues work toward publication of a manuscript.

There have also been challenges in manuscript being accepted for publication. The team initially submitted to *Molecular Psychiatry*, then *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, and is currently pursuing *Neuropsychopharmacology*. Based on peer reviews, the team has edited the manuscript and is hopeful of acceptance for publication soon.

There have been no changes that have impacted on expenditures of this project. There have been no significant changes that have impacted the use of animals involving this project.

5.4 AS170014-A6 Lofexidine Combined with Buprenorphine for Reducing Symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans

Subjects are recruited from the Michael E. DeBakey Opioid Treatment Program (OTP) roster. Most of these patients have pre-existing comorbidities, some of which require the prescription of protocol-prohibited medications. The research team has since evaluated a list of frequently prescribed medications, including dosages, and now has a revised list of allowable medications. This modification to the protocol will now allow recruitment of a subset of veterans who were previously excluded (without impacting outcomes or protocol safety).

As the above was being worked through, the research team encountered several protocol deviations relating to the eligibility of study participants and visits occurring out of the permissible window. A summary of protocol deviations are as follows:

- Protocol deviations: Various visits for subjects 01G011, 01G015, 01G017-19 occurred outside of the 2-day visit window.
- The primary care physician of 1 subject (01G009) notified the MEDVAMC compliance office regarding the patient's enrollment in the study. The PCP raised a cause for concern regarding the lack of communication between the research group and primary care teams. The research team was asked to place a voluntary hold on enrollment until the concern was resolved. The MEDVAMC compliance office conducted a thorough examination of the research documents and did not find any compliance issues. The research team submitted a plan of action to the MEDVAMC compliance office to prevent future lapses in communication between primary care teams and the research group. Although the research team was able to resolve all issues associated with the “Cause for concern,” this caused a one-month delay in screening and recruitment.
- On 05/03/2022, the research team was advised by the VA research pharmacy to halt the enrollment of new LFX subjects pending the recertification results of placebo tablets. Examinations and testing of the placebo tablets did not yield recertification, which caused a one-month delay in enrollment. As a result of the non-recertification of placebo tables, the VA research pharmacy reconfigured how the study medication and matching placebo were prepared, and consequent IRB amendment submitted detailing this change. Enrollment for new LFX subjects resumed on 06/16/2022.

On 06/03/2022, the research team was notified by a representative from US World Meds of the non-recertification of placebo tablets. As a result, the research team has incurred additional expenses related to the reconfiguration of the placebo tablets. A detailed explanation of expenses can be found below:

Research Pharmacy charges: $35/100 capsules

Remaining Subjects to be recruited:	50
Max daily Capsules Needed	8/day
Study days over 12 weeks	84
Total capsules needed for remainder of study	33,600
Cost to encapsulate LFX tablets and matching placebo	$11,760

5.5 AS170014-A7 Effect of Sublingual Formulation of Dexmedetomidine HCl (BXCL501) on Ethanol in Heavy Drinkers with PTSD- Alcohol Interaction Study

The study team initially struggled with slow enrollment. However, the team has since pursued protocol amendments altering inclusion criteria such as age, PTSD threshold, and most recently heartrate in an effort to broaden the patient population to pull from. They also increased advertisement efforts via craigslist and partnered with TrialFacts to help engage willing, eligible participants. Once the study team complete 10 subjects in Study 1 the study team will then be able to take the next steps with the FDA for getting items aligned for Study 2 of this project to move forward.

5.6 AS170014-A8 Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy

The study team had had difficulty with their IV self-administration study with the catheters not remaining functional; however, they have changed to oral self-administration to enable them to achieve the goals of AIM 1.

5.7 AS170014-A10 Leveraging multi-omic data integration for in silico compound prioritization

The study team is expecting a shift in staffing in the next quarter but does not expect this to delay the progression of study aims.

6. Products

6.0 PASA Management

Specific products that have resulted from these projects during the reporting period include conference papers and presentations and publications.

Presentations

Presentations are as noted below.

Publications

Publications are as noted below.

6.1 AS170014-A1 Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy
The study team delivered the presentation described below:

> *'Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-fentanyl Vaccine and Buprenorphine Combination Therapy, Colin N. Haile, Alcohol and Substance Use IPR 09/23/2021'*

Most recently, the study team submitted an article to the *Pharmaceutics* Journal.

6.2 AS170014-A2 Pre-clinical assessment of PT150 for opioid use disorder and PTSD
One presentation of results from Aim 1 to Military Operational Medicine Research Program (MOMRP) annual meeting was given called "Effects of the glucocorticoid receptor antagonist PT150 on stress-induced fentanyl seeking in male and female rats." Additionally, one scientific article was published, and one manuscript was prepared:

> *'Hammerslag, L. R., Denehy, E. D., Carper, B., Nolan, T. L., Prendergast, M. A. and 9 Bardo, M. T. (in press). Effects of the glucocorticoid receptor antagonist PT150 on stress-induced fentanyl seeking in male and female rats. Psychopharmacology. [**PMCID in progress**].'*
>
> *'Bardo, M. T., Chandler, C. Denehy, E. D., Carper, B., Prendergast, M. A. and Nolen, T. L. Effect of the glucocorticoid receptor antagonist PT150 on fentanyl self-administration in rats following early life stress. Manuscript in preparation.'*

6.3 AS170014-A5 Pre-clinical testing of FKBP5 Inhibitors for alcohol use disorder-PTSD comorbidity
Dr. Bryan Cruz presented at the Research Society on Alcoholism annual meeting (June 2022). See citation below.

> *'Cruz B, Vozella V, Xu J, Kirson D, Carper B, Hirsch S, Bradley L, Fain K, Nolen T, Kosten T, Crawford M, Kosten T, Zorrilla EP, & Roberto M. Benztropine, FKBP5 Inhibitors Modulate Alcohol Drinking and Trauma-Related Behaviors in a model of Comorbid Post-Traumatic Stress and Alcohol Use Disorder (June 2022). Research Society on Alcoholism, Virtual Meeting.'*

The study team has drafted and submitted a manuscript to most recently to *Neuropsychopharmacology* and awaits acceptance for publication.

6.4 AS170014-A6 Lofexidine Combined with Buprenorphine for Reducing Symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans
The project is newly started, and no products have been reported at this time.

6.5 AS170014-A7 Effect of Sublingual Formulation of Dexmedetomidine HCl (BXCL501) on Ethanol in Heavy Drinkers with PTSD- Alcohol Interaction Study
Project is still actively recruiting participants, and no products have been reported at this time..

6.6 AS170014-A8 Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy
The following manuscripts were published:

'Colin N. Haile, Miah D. Baker, Sergio A. Sanchez, Carlos A. Lopez-Arteaga, Anantha L. Duddupudi, Gregory D. Cuny, Elizabeth B. Norton, Thomas R. Kosten, Therese A. Kosten, An immunoconjugate vaccine alters distribution and reduces the antinociceptive, behavioral and physiological effects of fentanyl in male and female rats. ***Pharmaceutics, (under review), 2022.'***

*'Colin N. Haile, Miah D. Baker, Sergio A. Sanchez, Anantha L. Duddupudi, Gregory D. Cuny, Elizabeth B. Norton, Thomas R. Kosten, Therese A. Kosten, An anti-fentanyl conjugate vaccine alone and in combination with buprenorphine attenuates fentanyl-induced antinociception and distribution. [****In preparation].'***

Working under the current patent application:

Haile CN, Cuny GD, Norton EB, Kosten TA. Adjuvanted conjugate opioid vaccine, (5/27/2020).

6.7 AS170014-A10 Leveraging multi-omic data integration for in silico compound prioritization

An abstract summarizing data integration and repurposing candidate identification pipeline was accepted for a poster presentation at the American Society of Human Genetics (ASHG) annual meeting in October 2022.

'Stratford J, Carnes MU, Schu M, Quach BC, Willis C, Mathur R, Johnson EO, Carter J, Nolen TL, Vandergrift N, Kosten T, Webb BT. Identifying compounds to treat opiate use disorder by leveraging multi-omic data integration and multiple drug repurposing databases.'

The study team has also produced a pilot R Shiny app as a proof of principle with the goal of making the final catalog of results easily accessible and searchable. Currently, this is only being tested internally and is not ready for public access.

7. Participants and Other Collaborating Organizations

PASA DCC and Management (out of RTI International)

Nolen, Tracy	Principal Investigator	11%
Vandergrift, Nathan	Co-Principal Investigator	6%
Bradley, Lauren	Research Coordinator	5%
Arafat, Dana	Financial/Subcontracts Manager	14%
Carper, Ben	Statistician	5%
Crawford, Meg	Research Coordinator	8%
Coggburn, Katie	Research Coordinator	16%
Hirsch, Shawn	Statistician	11%
Williams, Alexis	Research Coordinator	7%
Smith, Emily	System Analyst	10%
Tang, Yan	Programmer/Analyst	4%
Turner, Gene	Clinical Data Manager	20%
Whitworth, Ryan	Statistician	14%
Hemphill, Martin	Financial Analyst	1%
Hudspeth, Julie	Financial Analyst	1%
Lewis-Evans, Dawn	Project Coordinator	2%
Pickett, James	Programmer/Analyst	1%

Thomas, Brittany	System Analyst	1%
Williams, Kristi	Research Coordinator	3%

Baylor College of Medicine (PASA Management)

Kosten, Thomas	PI/PD	25%
Domingo, Coreen	Key Personnel	75%

RTI International

Leveraging Multi-omic Data Integration for In-Silico Compound Prioritization

Webb, Todd	Principal Investigator	18%
Mathur, Ravi	Co-Investigator	7%
Quach, Bryan	Co-Investigator	6%
Carnes, Megan	Co-Investigator	4%
Schu, Matthew	Co-Investigator	3%
Johnson, Eric	Co-Investigator	1%
Changar, Cynthia	Project Specialist	1%
Stratford, Jeran	Staff Scientist	8%
Willis, Caryn, MS	Bioinformatician	13%

University of Houston

Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy

Haile, Colin	Principal Investigator	75%
Kosten, Therese	Co-Principal Investigator	25%
Cuny, Greg	Co-Investigator	25%
Arteaga, Carlos	Research Technician	75%
Baker, Miah	Research Technician	75%
Duddupudi, Anantha	Post Doc	16%

The Scripps Research Institute*

Pre-clinical testing of FKBP5 inhibitors for alcohol use disorder-PTSD comorbidity

Roberto, Marisa	Principal Investigator	5%
Zorrilla, Eric	Co-Investigator	5%
Cruz, Bryan	Study Coordinator	100% (no cost)
Vozella, Valentina	Post doc	50%

*Subcontract ended on 03/31/2022. However, the above numbers are included because it was the effort reported when the contract was still in effect (which is still within this reporting period for this FY.

Baylor College of Medicine

Assessing Lofexidine combined with buprenorphine for reducing symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans (LFX)

Verrico, Christopher	Principal Investigator	50%
Kosten, Thomas	Co-Principal Investigator	25%
Fermo, John	Co-Investigator	100%
Sibley, Alexandra	Co-Investigator	58%
Asif Khan, Mohammad	Co-Investigator	100%
Vaughan, Adetola	Study Coordinator	50%

Chii, Philip	Study Clinician	100%
Moukaddam, Nidal	Co-Investigator	58%

Yale University

Developing a proof-of-concept clinical trial to evaluate the use of a safe and highly selective a2a Adrenergic Receptor Agonist, BXCL 501, for the treatment of ASUD comorbid with PTSD and/or TBI – Planning Grant

Petrakis, Ismene	Co-Principal Investigator	20%
Krystal, John	Co-Principal Investigator	1.5%
Levy, Lucienne	Research Assistant	10%
Emily Pisani	Coordinator/RA	50%
Jane, Jane Serrita	Psychologist	25%

7.1 AS17004-A1 Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy

7.1.a. Individuals who have worked on the project include:

Dr. Colin Haile (PI): He directed all phases of the study including but limited to conducting experiments, generating, and interpreting data, animal protocol approval, providing updates and disseminating results. Dr Kosten has provided input into the design of the studies. Dr. Cuny with his post-doc Dr. Duddupudi synthesized the conjugate vaccine. Mr. Quadri and Ms. Baker conducted experiments and utilized numerous types of ELISA assays for fentanyl and anti-fentanyl antibody quantification.
Miah Baker (RA): Contributed by helping to conduct vaccination experiments, collect bloods, analgesic tests and process brain and blood samples, protein estimation and ELISAs.
Anantha Duddupudi (Post-Doctoral Fellow): Synthesis optimization of the anti-fentanyl conjugate vaccine.
Saif Quadri (RA): Contributed by helping process brain and blood samples, protein estimation and ELISAs.

7.1.b. Change in other active support for active support of PIs

The PI obtained additional funding (expansion) in previous reporting period to conduct additional experiments and produce clinical grade vaccine for a potential Phase 1 Clinical Trial. No other change has been noted.

7.1.c. Other organizations that have been involved as partners:

Dr. Norton, Tulane University School of Medicine, provided expert guidance and provided the adjuvant for the study (dmLT).

7.2 AS170014-A2 Pre-clinical assessment of PT-150 for opioid use disorder and PTSD

7.2.a. Individuals who have worked on the project include:

Dr. Michael Bardo (PI): Academic salary charge; no change
Dr. Mark Prendergast (Co-I): No change.
Dr. Craig Rush (Co-I): No change.

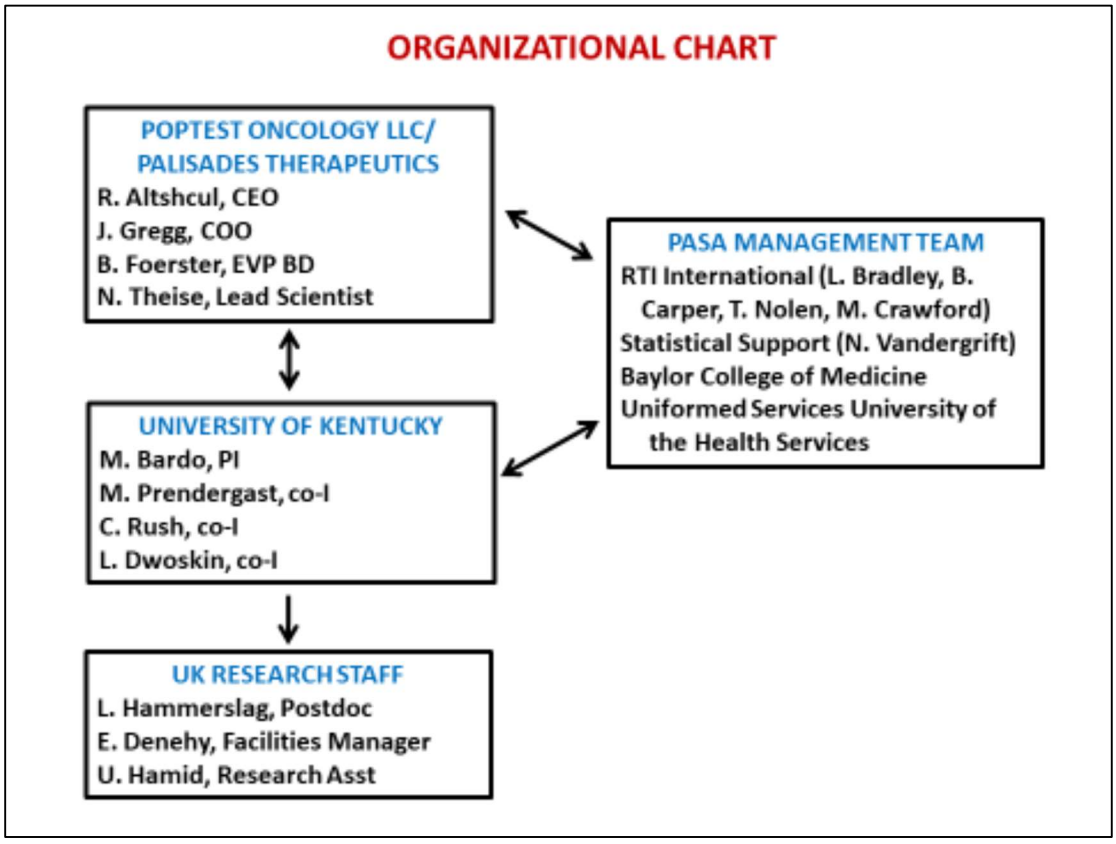
Dr. Linda Dwoskin (Co-I): No change.
Ms. Emily Denehy (Facilities Manager): No change.
Dr. Cassie Chandler (Postdoc): Effort ended November 2021

7.2.b. Change in other active support for active support of PIs

Previously funded grants:
NIH R01 DA053070
Bardo (mPI with Turner and Ortinski)
03/15/2021-02/31/2024
Functional and genomic signatures of escalated fentanyl use
Role: mPI

NIH U01 DA051377
Prisinzano (PI)
09/01/2021-07/31/2024
Development of agents for synthetic opioid overdose
Role: co-I

7.2.c. Other organizations that have been involved as partners:



7.3 AS170014-A5 Pre-clinical testing of FKBP5 Inhibitors for alcohol use disorder-PTSD comorbidity

7.3.a. Individuals who have worked on the project include:

Dr. Marissa Roberto (PI): Study experiments have concluded, and the study recently had a manuscript accepted for publication in Experimental and Clinical Psychopharmacology.
Dr. Eric Zorrilla (Co-PI): Efforts ended in May 2022
Dr. Michal Bajo (Co-PI): Efforts ended in May 2022
Dr. Bryan Cruz (Study Coordinator): Efforts ended in May 2022
Dr. Valentina Vozella (Study Coordinator): Efforts ended in May 2022
Dr. Kerry Ressler (Consultant): Efforts ended in May 2022

7.4 AS170014-A6 Lofexidine Combined with Buprenorphine for Reducing Symptoms of Post-Traumatic Stress Disorder and Opioid Use Relapse in Veterans

7.4.a. Individuals who have worked on the project include:

Dr. Christopher Verrico (PI): Responsible for all trial activates conducted at the Michael E. DeBakey VA Hospital and Baylor College of Medicine; responsible for reviewing and confirming participant eligibility.
Dr. Thomas Kosten (Co-PI): Responsible for performing and overseeing study related procedures; responsible for making important study related decisions in compliance with the ethical conduct of the study.
Ms. Adetola Vaughan (Study coordinator): Responsible for managing day-to-day conduct of the study; responsible for ensuring that the research is conducted in compliance with the study protocol as well as federal, state, and institutional guidelines and regulations; responsible for making changes to the IRB and communicating changes to the IRB.
Dr. Philip Chii (Study Clinician): Responsible for obtaining medical history; conducting screening and post study physical exams; evaluates study related test results; responsible for assessing adverse events.
Dr. John Fermo (Co-I): Responsible for making study related medical decisions; responsible to assessing adverse events and serious adverse events.
Dr. Fang Yang (Co-I): Responsible for making study related medical decisions; responsible to assessing adverse events and serious adverse events.
Dr. Mohammad Asif Khan (Co-I): Responsible for making study related medical decisions; responsible to assessing adverse events and serious adverse events.
Dr. Alexandra Sibley (Co-I): Responsible for obtaining medical history; conducting screening and post study physical exams; evaluates study related test results; responsible for assessing adverse events.
Dr. Nidal Moukaddam (Co-I): Responsible for making study related medical decisions; referring suboxone patients for recruitment; responsible to assessing adverse events and Serious adverse events.

7.5 AS170014-A7 Effect of Sublingual Formulation of Dexmedetomidine HCl (BXCL501) on Ethanol in Heavy Drinkers with PTSD- Alcohol Interaction Study

7.5.a. Individuals who have worked on the project include:

Dr. Ismene Petrakis (Co-PI): no change

Dr. John Krystal (Co-PI): no change
Ms. Lucienne Levy (Research Assistant): no change
Ms. Emily Pisani (Coordinator/RA): no change

7.5.b. Other organizations that have been involved as partners:
BioXcel Therapeutics, Inc remains partners in this study.

7.6 AS170014-A8 Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy

7.6.a. Individuals who have worked on the project include:
Dr. Colin Haile (PI): Direct all phases of the study including but not limited to conducting experiments, generating and interpreting data, animal protocol approval, providing updates, and disseminating results.
Dr. Thomas Kosten (Co-I): Provides input into the design of the studies and manuscript preparation.
Dr. Greg Cuny (Co-I): Synthesizes the conjugate vaccine.
Dr. Anantha Duddupudi (Postdoc): Assists with synthesis of the conjugate vaccine.
Mr. Carlos Arteaga (Research Technician): Conducts behavioral experiments and utilized numerous types of ELISA assays for fentanyl and anti- fentanyl antibody quantification.
Ms. Miah Baker (Research Technician): Conducts behavioral experiments and utilized numerous types of ELISA assays for fentanyl and anti- fentanyl antibody quantification.

7.6.b. Other organizations that have been involved as partners:
Dr. Norton, Tulane University College of Medicine remains to provide expert guidance and the adjuvant for the studies (dmLT).

7.7 AS170014-A10 Leveraging multi-omic data integration for in silico compound prioritization

7.7.a. Individuals who have worked on the project include:
Dr. B. Todd Webb (PI): Responsible for supervising overall project activities including study design, monitoring progress of small group aim specific working groups, and adjusting goals based on interim results.
Dr. Ravi Mathur (Co-I): Responsible for performing aim 1 related objectives including GWAS data collection and GenomicSEM analyses.
Dr. Bryan Quach (Co-I): Responsible for overseeing and performing aim 2 related objectives and analyses including gene expression meta and integrated network analyses.
Dr. Jeran Stratford (Co-I): Responsible for performing aim 3 related objectives and analyses including drug database querying, data integration, R shiny app development, and disseminating results.
Dr. Matt Schu (Co-I): Responsible for supporting aim 3 objectives including developing semi-automated querying of drug repurposing databases. Also assisting in managing and planning staff effort across project aims.
Dr. Megan Carnes (Co-I): Responsible for supporting aim 3 objectives including drug database querying, data integration design, and gene ranking algorithm development.
Ms. Caryn Willis (Bioinformatics Analyst): Supports aim 2 related objectives and analyses including performing gene expression meta and integrated network analyses.

7.7.b. Change in other active support of PI/PD or senior/key personnel since last reporting period:

- Two co-investigators, Matt Schu and Megan Carnes, were originally budgeted for 12.5% (1.5 CM) and 15% (1.8 CM) effort, respectively. During year 1, both had unforeseen increases in commitments outside this project. Jeran Stratford (PhD) was added to the team to increase capacity related to Aim 3 including drug database integration and building a R based Shiny app to query the results. This reallocation of effort from Drs. Schu and Carnes to Dr. Stratford will continue in year 2.
- Co-investigator Bryan Quach was recently awarded a NIH funded diversity supplement intended to advance career development. The award requires Dr. Quach to focus 75% of his effort to this new award. Based on the new award requirements and other commitment, we anticipate a reduction in effort from 15% to 5% for year 2 project period. RTI's Genomics, Bioinformatics, and Translational Research Center (GOBOT) has recently recruited two PhDs with expertise and skills that can contribute to this project and offset the planned reduction in effort from Dr. Quach.