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TITLE: Alcohol and Substance Abuse Disorders Research Program Consortium Award

PRINCIPAL INVESTIGATOR: Tracy Nolan

CONTRACTING ORGANIZATION:

Research Triangle Institute
Research Triangle Park, NC
27709

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14. ABSTRACT

The goal of the PASA Consortium is to fund research that aims to identify and develop new medications to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially those that occur concurrently with traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). In the first year, the consortium established infrastructure for PASA 2 and awarded the first 2 studies as planning grants. A second request for applications was launched in March 2019 and two planning grants were selected for funding.

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Table of Contents

1. Introduction

The goal of the PASA Consortium is to fund research that aims to identify and develop new medications to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially those that occur concurrently with traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). Clinical trials that include military service member and Veteran populations are highly desirable because this comorbidity, along with mild to moderate TBI, is 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 the PASA Consortium.

The PASA Consortium 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 as manifested in PTSD or TBI. The three broad aims are:

AIM 1. Discover novel medications and combination medications for ASUD

AIM 2. Develop these medications through a rational Phase I proof of concept pipeline

AIM 3. Conduct Phase II preliminary safety and efficacy trials of potential medication combinations in optimal target populations and explore functional genetic polymorphisms for matching patients to these medications.

2. Keywords

- alcohol and substance use disorders
- post-traumatic stress disorder
- traumatic brain injury
- request for applications
- pharmacotherapy
- research consortium

3. Accomplishments

Our primary objectives for the first year were to:

- Establish PASA2 award
- Establish RTI's infrastructure for the initiation of PASA2
- Complete the SRPP RFA selection process to select the first PASA2 studies
- Complete revision of the PASA Manual of Operations (MOO)

RTI was awarded PASA2 on September 15, 2018. The infrastructure for PASA2 is in place and largely is based upon the existing infrastructure of PASA1 with respect to using shared staffing and resources (e.g.

the PASA website, electronic data capture system, DSMB) across PASA contracts. The revised MOO was submitted to GOR on 01/31/2019.

To select the first studies for PASA2, RTI completed the review of RFA #3a for small-cost and short duration planning grants to develop clinical trials and 3b for full study implementation awards for pre-clinical studies or clinical trials (conducted under PASA1). Thirteen applications were received in response to our solicitations. Four awards were recommended to the GSC for funding including two planning grants under PASA1 and two pre-clinical studies = under PASA2 on 11/30/2018

1. AS170014-A1 Novel Strategies for the Treatment of Opioid Use Disorder and Post-Traumatic Stress Disorder: Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy
2. AS170014-A2 Preclinical assessment of PT-150 for opioid use disorder and PTSD

In March 2019, a second request for applications was released under PASA2 for small-cost and short-duration planning grants to develop clinical trials (RFA 4a) and for full study implementation awards for pre-clinical studies (RFA 4b). The option for full study awards for clinical trials was removed from this round, as prior submissions for full study awards for clinical trials were consistently found to have major deficiencies particularly with respect to meeting regulatory requirements for researching investigational new drugs that could be best addressed during a planning grant. Five applications were received for RFA 4a and 10 for the RFA 4b. Two planning grants were recommended for funding on 08/05/2019 and 1 pre-clinical study was recommended for funding on 09/26/2019 and subcontracting is in process for all 3 studies.

3.1 Discovery Studies

3.1.1 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 to support the development of an anti-fentanyl vaccine targeting fentanyl assessed 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..1a Primary Objectives and milestones for the first year were:

1) Optimize the new formulation of our fentanyl vaccine (achieved).
2) Optimize the synthesis protocol for the fentanyl vaccine (achieved).
3) Begin vaccinating animals (planned)

3.1.1.b Accomplishments under the goals include:

The original proposed period for this grant was 01/01/2019-12/31/2019 but was extended to 3/31/2020 to account for time required to get subcontracts in place. . To avoid delays, the research requested interim funding from their institution to support activities until the subcontract was in place and the associated costs could be invoiced through the PASA2 subcontract. To date, the following work has been completed:

- UH Animal protocol initial approval 02/02/2019, amendment to add an additional vaccine formulation approved 05/06/2019.
- Batches of two vaccine formulations synthesized 02/2019, synthesis optimization-ongoing
- Interim funding requested to purchase supplies approved 02/08/2019.
- Established collaboration with Fina BioSolutions to provide carrier protein 03/2019.
- -Established collaboration with Tulane to provide adjuvant 03/26/2019.
- Interim funding requested for salaries approved 5/30/2019.
- Trained new graduate student that will be working on this project 04/2019-05/2019.
- Fractions analyzed to identify and quantitate carrier protein 04/24/2019, 05/16/2019,05/30/2019,06/12/2019,06/13/2019.
- Fractions analyzed confirmed successful conjugation of carrier protein to hapten 05/04/2019.
- ACURO Animal protocol initial approval 05/08/2019, amendment to add an additional vaccine formulation approved 06/20/2019.
- Research assistant for this project hired 06/01/2019.
- Experiments conducted to address DEA concerns our fentanyl hapten may have biological activity 07/27/2019 (see below)
- Confirmation the new vaccine formulation generates anti-fentanyl antibodies in mice 08/20/2019 (see below).
- Optimized conjugate synthesized (FEN-CRM197) to be used for experiments in AIM1 and AIM2 purified for vaccination 09/12/2019
- At present, approximately 50 rats have been used in experiments for AIM3 10/04/2019

Data from two critical experiments conducted that demonstrate 1) that our new vaccine synthesis generates a viable conjugate product (Figure 1A), 2) produces anti-fentanyl antibodies in mice (Figure 1B) and 3) our hapten shows no analgesic activity when compared to fentanyl (Figure 2A-D).

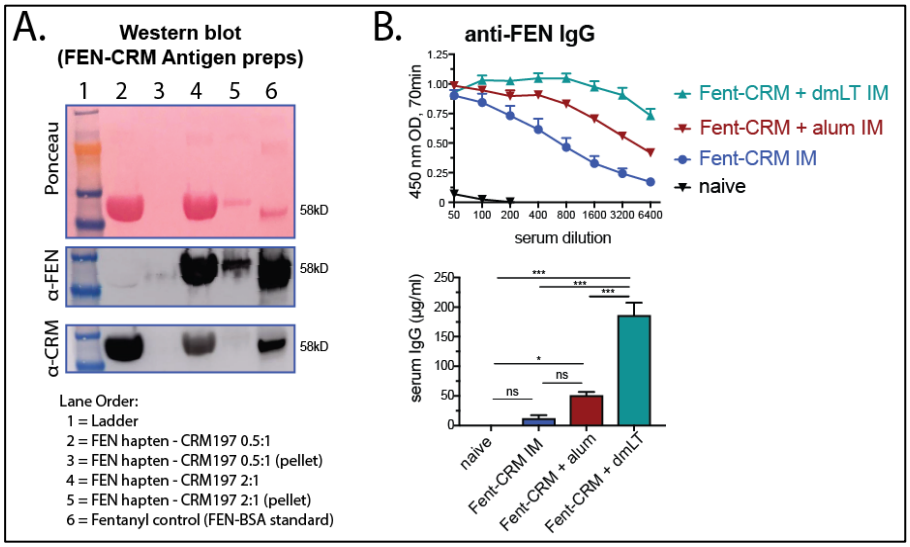


Figure 1. FEN-$_{Eco}$CRM immunogen evaluation by Western Blot and mouse immunogenicity. FEN hapten-CRM conjugates were prepared at different FEN hapten:CRM carrier ratios [e.g. 0.5 or 2.0 mols of FEN per mol CRM exposed lysine residues with the ratio of FEN hapten to coupling reagents remaining at 1:1]. (A) Test formulations were evaluated by SDS-PAGE/Western blot in comparison with FEN-BSA control by Ponceau staining (for all proteins), binding of anti-Fentanyl antibodies (α-FEN) or stripped and re-probed for ant-CRM197 antibodies (α-CRM) with brightfield and chemiluminescence overlay images shown. (B) 2:1 FEN-CRM formulation was dialyzed and used to immunize groups of Balb/c mice (n=5) on days 0, 14 at 1.5µg per mouse intramuscularly injected in 20 µl alone in PBS buffer or with absorption 1:1 with 2% alyhydrogel (alum, 100µg final dose) or admixed with 1µg dmLT. Anti-fentanyl serum IgG antibody levels were analyzed by ELISA 7 days post-boost using alternate carrier antigen protein (e.g., tetanus toxoid-Fentanyl) with raw data (top) and analyzed data (bottom) are shown.

Lack of Analgesic Effects of Haptens in Rodents: There has been some concern that haptens with similar structure to the parent compound, in this case FEN, may harbor some intrinsic biological activity, which would significantly hinder the development and production of clinical grade vaccine. To verify the lack of activity of our FEN hapten, we evaluated whether administration of our FEN hapten (5-HAP) possessed antinociceptive effects. We conduced analgesic tests using the tail flick assay testing dose concentrations comparable to that of fentanyl administered IP. Data generated from tail flick analgesic tests for fentanyl citrate are presented in Figure 2A and B. Analysis following ANOVA yielded a significant Drug ($F_{(1,39)}$, 62.21, P<0.001), Dose ($F_{(3,39)}$, 10.09, P<0.001) and DrugXDose interaction ($F_{(3,39)}$, 18.35, P<0.001). Pairwise multiple comparisons indicated significant differences between saline and fentanyl citrate latencies for doses 0.1 (P<0.05), 1 (P<0.001) and 10 (P<0.001) ug/kg (Figure 2 A.). Regression analysis of %MPE and each fentanyl citrate dose yielded a near perfect relationship (Figure 2 B.). Data generated from tail flick analgesic tests for 5-HAP are presented in Figure 2C and D. Analysis following ANOVA showed no statistically significant differences between saline and various doses of 5-HAP (P's>0.05). Regression analysis of %MPE and each 5-HAP dose suggested no relationship (Figure 2D.). Mice in all groups following 5-HAP administration showed no analgesic responses and no adverse effects.

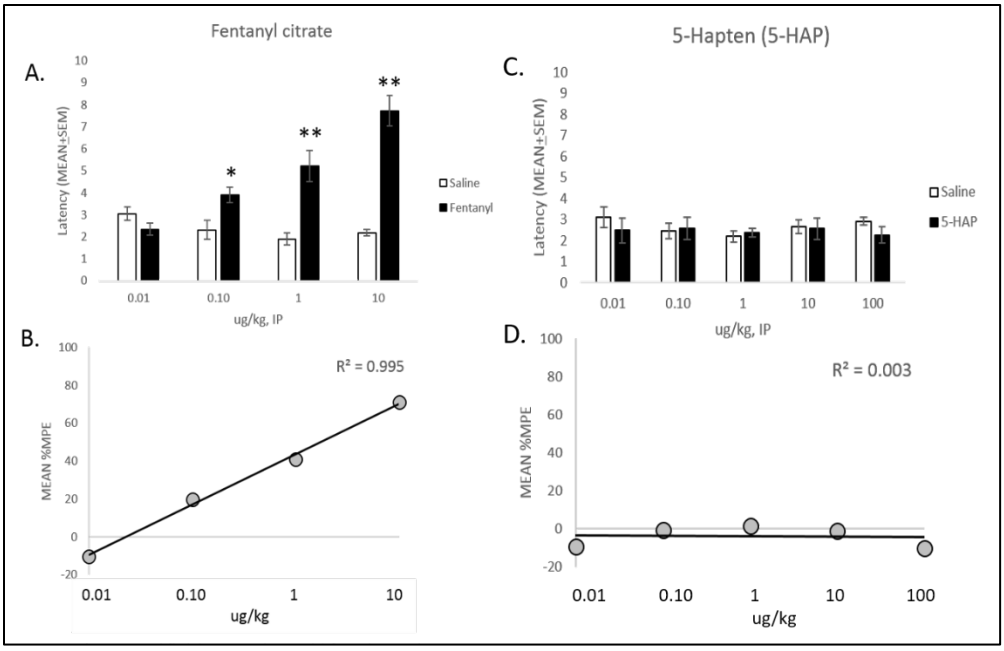


Figure 2. FEN Hapten (5-HAP) lacks intrinsic biological activity of fentanyl. Tail flick latencies (seconds) for saline and fentanyl citrate (A.) and relationship between drug dose and mean %MPE (B.) and tail flick latencies for saline and 5-HAP (5-Hapten, C.) and relationship between drug dose and mean %MPE (D.). Fentanyl citrate vs. saline *<0.05, **<0.001.

3.1.1.c Training and professional development provided:

Adopting new techniques to purify and concentrate vaccine preparations offered opportunity to learn new skills.

3.1.1.d Dissemination to communities of interest:

Through email and weekly conference calls.

3.1.1.e Plans for next reporting period to accomplish goals and objectives:

We plan to move forward with conducting the experiments proposed in the application. With our vaccine now optimized, rats will be vaccinated to achieve AIMs 1 and 2. We will continue to conduct experiments associated with AIM 3.

3.2.1 AS170014-A2 Preclinical assessment of PT-150 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 preclinical study is that selective blockade of glucocorticoid receptors (GRs) in the brain with PT-150 will serve as an effective pharmacotherapy for OUD and co-morbid PTSD. In Aim 1, we are determining if PT-150 (0, 50 or 100 mg/kg, p.o.) reduces stress-induced reinstatement of fentanyl seeking using a reinstatement model of relapse in rats. Stress is being applied either environmentally (mild footshock) or pharmacologically (yohimbine) and reinstatement of fentanyl seeking is being measured. In Aim 2 (not yet started), we will determine if PT-150

reduces fentanyl self-administration in individuals with co-morbid PTSD. Rats will be exposed to two different models of stress: (1) chronic social isolation and (2) acute stress induced by restraint/swim, which have been used to model PTSD. This aim will determine if oral PT-150 reduces the effects of chronic social isolation and acute stress, either alone or in combination, on fentanyl self-administration.

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

There are two major goals for this project as outlined below:

- Goal 1: Determine if PT-150 reduces stress-induced reinstatement of fentanyl seeking. In an ongoing experiment, male and female rats are being trained to self-inject escalating doses of the potent opioid fentanyl using a standard 2-lever operant conditioning procedure. Following this, rats are being treated daily with either PT-150 or placebo while undergoing response extinction (abstinence). Stress is then being applied either environmentally (mild footshock) or pharmacologically (yohimbine) and reinstatement of fentanyl seeking is being measured. The main objective of this experiment is to test the hypothesis is that PT-150 will reduce stress-induced reinstatement of fentanyl seeking.
- Goal 2: Determine if PT-150 reduces fentanyl self-administration in individuals with co-morbid PTSD. In a planned experiment, rats will be raised in either social isolation or in group housing and then will receive acute restraint/swim stress or control treatment. Previous work has shown that these stressful manipulations increase drug self-administration behavior. 4

Plasma corticosterone will be measured immediately before and after the acute stress. On the day after the acute stress treatment, rats will be treated daily with either PT-150 or placebo and then will be trained to voluntarily self-administer i.v. fentanyl using a standard 2-lever operant conditioning procedure. The main objective of this experiment will be to test the hypothesis that PT-150 will reduce the stress-induced increase in fentanyl self-administration.

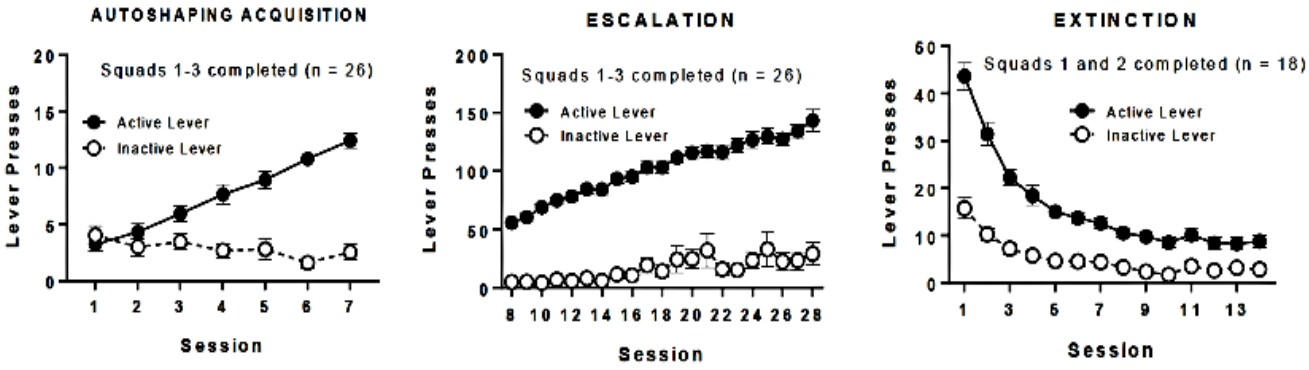
3.2.1.b Accomplishments under the goals include:

Goal 1: Determine if PT-150 reduces stress-induced reinstatement of fentanyl seeking. The major activities accomplished under this goal are as follows:

a) Quality Assurance Plan (QAP) completed and approved.
b) Manual of Operatives (MOP) completed and approved.
c) Institutional Animal Care and Use Committee (IACUC) protocol at University of Kentucky completed and approved.
d) Animal Care and Use Review Office (ACURO) protocol at US Department of Army completed and approved.
e) Account funds set up at the University of Kentucky.
f) Purchase, install and confirm foot shock grids used in Goal 1 were functional.
g) Prepare timeline for completion of experiment for Goal 1.
h) Begin experiment, consisting of 5 squads of rats (n= 12 per squad; 6 male and 6 female). Each squad is being run through 6 phases in the experiment and progress for each squad is outlined in the table below:

Squad	Surgery (implant catheter)	Autoshaping (1 hr session)	Escalation (6 hr session)	Abstinence	Extinction (start PT-150 treatment)	Reinstatement (yohimbine and footshock)
1	x	x	x	x	x	x
2	x	x	x	x	x	
3		x	x	x		
4			x			
5						

Graph results to date. While a full statistical analysis will await final data collection, a graphical presentation of the results are clearly illustrating that rats are: (1) acquiring fentanyl self-administration using the proposed autoshaping procedure in 1 hr sessions; (2) escalating fentanyl self-administration across repeated 6-hr sessions; and (3) showing extinction of responding across 1 hr sessions (collapsed across PT-150 treatment condition). These findings are illustrated in the graphs below (data incomplete):



Goal 2: Determine if PT-150 reduces fentanyl self-administration in individuals with co-morbid PTSD. Experiment not started.

3.2.1.c Training and professional development provided:

Dr. Lindsey Hammerslag on the University of Kentucky team has been on the bi-weekly teleconferences with the staff of RTI. She has been afforded the opportunity to gain insight into the workings of an independent nonprofit institute that provides research, development, and technical services to academic, government and commercial entities worldwide

3.2.1.d Dissemination to communities of interest:

Results from this work is not ready for dissemination.

3.2.1.e Plans for next reporting period to accomplish goals and objectives:

Continue to add subjects to Aim 1 and initiate Aim 2.

3.3 Administrative Deliverables

We executed subcontracts for the University of Houston and University of Kentucky. We submitted all quarterly reports and continued to hold weekly meetings with PASA leadership and with CDMRP and distribute meeting minutes.

3.4 RFA Release and Review

The PASA Study Research Planning Program (SRPP) finalized the selection of Research Funding Opportunities started with PASA1. The opportunities focused on:

- **Request for Application (RFA) #3a**: Small-cost and short-duration planning grants awarded to investigators concerning a specific compound or combination of compounds.
- **Request for Application (RFA) #3b**: Full study implementation awards for either:
    - Conduct of proof-of-principle basic research to determine which compounds are most appropriate for human research trials; or
    - Conduct of human proof-of-concept trials with promising compounds. The human trials must be ready-to-implement as defined in the RFA.

The SRPP finalized and released two additional Research Funding Opportunities in March 2019. The opportunities focused on:

- **Request for Application (RFA) #4a**: Small-cost and short-duration planning grant awarded to investigators concerning a specific compound or combination of compounds. Designed to determine the clinical development plan and associated clinical trials needed to advance the compound to FDA approval for ASUD treatment. The protocol for the first study will be developed as part of the planning grant and will be considered for funding and implementation by the PASA Consortium.
- **Request for Application (RFA) #4b**: Full study implementation awards for the conduct of proof-of-principle basic research to determine which compounds are most appropriate for human research trials.

Funding decisions will be announced during year 2.

4. Impact

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

Optimizing the synthesis of our FEN-CRM vaccine was an important success that may lead to significant impact once the vaccine is tested in humans.

4.2. AS170014-A2 Preclinical assessment of PT-150 for opioid use disorder and PTSD

Since no final results have been collected at this point, there are no conclusions or products to report at this time. However, if the results of this preclinical project provide initial proof-of-principle evidence that PT-150 ameliorates stress-induced escalation of fentanyl self-administration and stress-induced reinstatement, it would open a potential new avenue for treating co-morbid OUD and PTSD. Positive results from this study would form the basis of a robust laboratory study in humans conducted in

partnership with co-investigator Dr. Craig Rush at the University of Kentucky and the business entity holding rights to the drug (Palisades Therapeutics, a division of Pop Test Oncology LCC, Cliffside Park, NJ). Commercialization of this therapeutic would have widespread impact on treating veterans and other vulnerable populations who suffer from co-morbid OUD and PTSD.

5. Changes/Problems

The Consortium Project Director/Principal Investigator changed from Dr. Rick Williams to Dr. Tracy Nolen in August 2019. Dr. Nolen is a senior research statistician in the Center for Clinical Research Network Coordination (CRNC) at RTI and has more than 16 years' experience in designing, implementing and analyzing pre-clinical research and clinical trials. Dr. Nolen was Principal Investigator (PI) for the Department of Defense (DoD) Chronic Effects of Neurotrauma Consortium (CENC) Biostatistics, Data Management and Study Management Core and served as a co-PI for the Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium. Rick Williams will continue as co-PI.

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

We have overcome the major obstacle of optimizing the synthesis of our vaccine. We do not foresee any further delay in completing experiments to achieve the AIMS.

5.2. AS170014-A2 Preclinical assessment of PT-150 for opioid use disorder and PTSD

a. Changes in approach and reasons for change.
No changes to report

b. Actual or anticipated problems or delays and actions or plans to resolve them.
We have experienced a slightly higher-than-anticipated number of casualties in the squads used for Aim 1 (our proposal estimated 20% attrition, and we have experienced 25% attrition). Initially, we had several very rare illness complications. Additionally, we have experienced slightly higher than normal levels of catheter failure due to a change in our surgical team requiring additional fine tuning of surgical techniques. If needed, we can always add one additional squad of rats into the design of Aim 1, although we do not currently anticipate that this will be necessary.

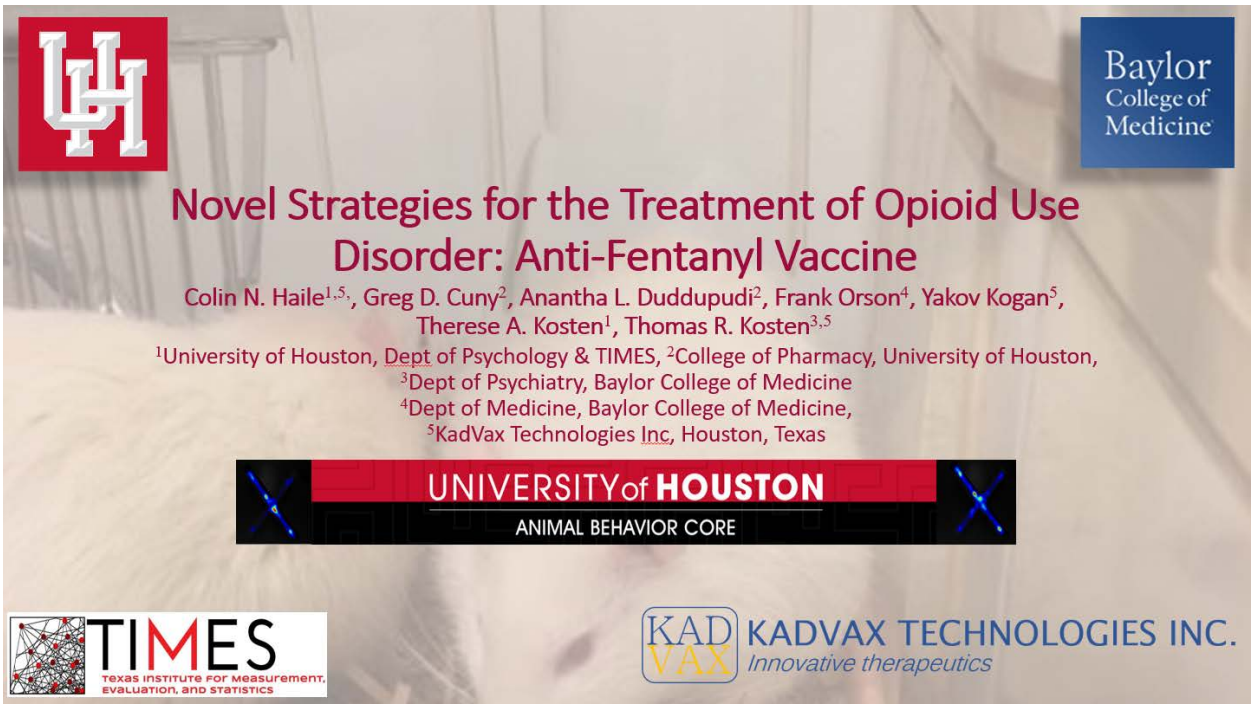
c. Changes that have a significant impact on expenditures.
If an additional squad of rats is required, this will increase cost accordingly.

d. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.
At this time, there have been no changes to the care, use, or number or animals or treatments used.

6. Products

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

The PI presented data at a meeting: College on Problems of Drug Dependence, San Antonio, TX 06/14/2019



6.2. AS170014-A2 Preclinical assessment of PT-150 for opioid use disorder and PTSD

No products have resulted from this project thus far.

7. Participants and Other Collaborating Organizations

RTI International - Management Core

Nolen, Tracy	Principal Investigator	11%
Williams, Rick	Co-Investigator	3%

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%
Sanchez, Sergio	Research Technician	75%
Baker, Miah	Research Technician	75%

University of Kentucky

Preclinical assessment of PT-150 for opioid use disorder and PTSD

Bardo, Michael	Principal Investigator	5%
Hammerslag, Lindsey	Post Doc	20%
Denehy, Emily	Facilities Manager	20%
Maggio, Sarah	Research Assistant	50%

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:

Miah Baker (2 months) Research Assistant. Contributed by helping to conduct vaccination experiments, collect bloods, analgesic tests.
Hailey Rodgers (2 months) Graduate student. Contributed by helping to conduct experiments described in AIM 2.
Sergio Sanchez (6 months) Research Assistant. Contributed by helping to conduct vaccination experiments, collect bloods, analgesic tests.
Anantha Duddupudi (4 months) Post-Doctoral Fellow. Synthesis optimization of the anti-fentanyl conjugate vaccine.

7.1.b. Change in active support of the PD/PIs or senior/key personnel since the last reporting period:

No change. This is the first reporting period for this grant.

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

Tulane University School of Medicine: characterization of the vaccine formulation.

7.2. AS170014-A2 Preclinical 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): 2 mo; Led the overall research in his laboratory. He was involved in the design and implementation of the work. He also reported to the PASA Management Core, prepared the IACUC and ACURO applications, and he managed the personnel in his laboratory.

Dr. Mark Prendergast (co-I): 1 mo; Served on the scientific advisory board at PopTest Oncology LLC/Palisades Therapeutics. He was responsible for providing the PT-150 for the work and served as consultant.

Dr. Craig Rush (co-I): 0.5 mo; Served as consultant for translating the results of the current preclinical project into a human laboratory study to assess the effects of PT-150 on opioid self-administration and craving.

Dr. Linda Dwoskin (co-I): 0.5 mo; Served as consultant for the connection between UK and PopTest Oncology LLC/Palisades Therapeutics to ensure that progress is made toward commercialization.
Dr. Lindsey Hammerslag (postdoc): 1 mo; Served to oversee data collection, data transfer and graphical presentation. She also assisted in surgeries, daily animal runs and participated in the bi-weekly teleconferences with RTI.

Ms. Emily Denehy (facilities manager): 4 mo; Served as the facilities manager who coordinated all ongoing studies in the laboratory of the PI. She was involved in surgical implantation of i.v. catheters, conducting and supervising day-to-day runs of the operant self-administration

sessions during the regular work week and data management. She also participated in the bi-weekly teleconferences with RTI.

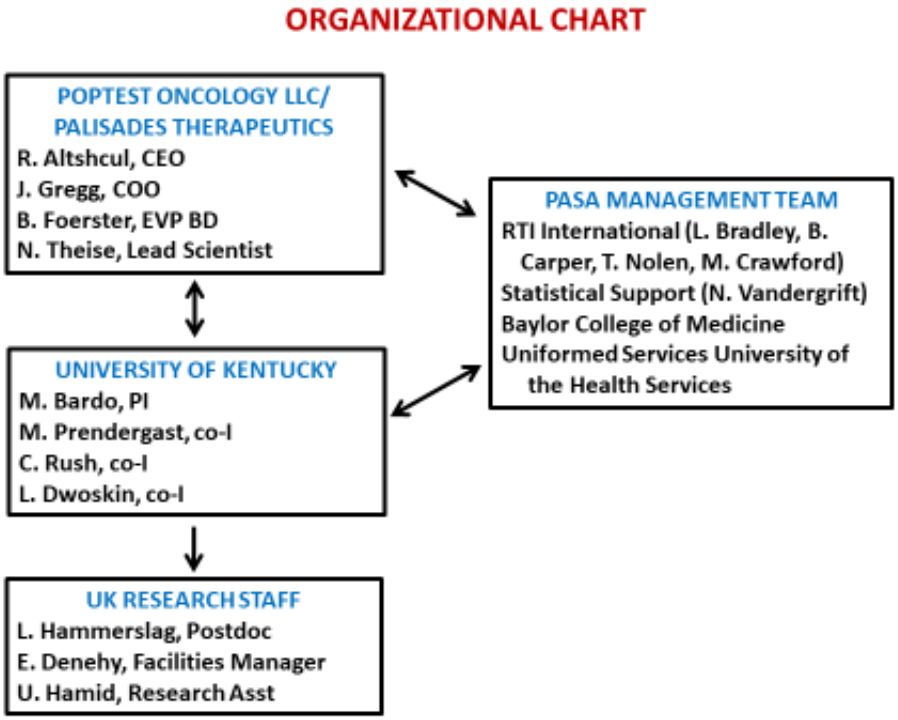
Mr. Usman Hamid (laboratory assistant): 1 mo; Served as part-time hourly employee whose primary responsibility was to run the operant self-administration session on the weekends.

7.2.b. Change in active support of the PD/PIs or senior/key personnel since the last reporting period:

No change in active support.

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

See organizational chart below:



DoD Alcohol and Substance Abuse Consortium Award

Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium

PI: Tracy Nolen, DrPh, Rick Williams, PhD & Thomas Kosten, MD **Org:** RTI International

Study Research Planning Program RFA #4

- Small-cost and short-duration planning grants to develop a clinical trial awarded to investigators concerning a specific compound or combination of compounds.
- Full study implementation awards for conduct of proof-of-principle basic research to determine which compounds are most appropriate for human research trials

The SRPP RFA #4 process netted 15 applications. Programmatic review is complete and studies will be awarded in Quarter 1 of Year 2.

Timeline and Cost

Activities	Q1	Q2	Q3	Q4
Consortium Set Up: Revised Manual of Operations				
Study review and selection for RFA#3a and 3b				
Release of RFA#4a and 4b, review and study selection				
Protocol development and study launch for two preclinical studies (AS170014-A1 and AS170014-A2)				
Ongoing data monitoring and clearning for two pre-clinical studies (AS170014-A1 and AS170014-				
Continued protocol development of the two planning grants (AS140026-A6 and A7)				
Costs per month	$7k	$42k	$68k	$226k
Total Costs: $344k to date; $6,750,000 remaining				

Year 1 Completed Objectives

- Competed programmatic review for second solicitation for short-duration planning grants and basic science research.
- Updated PASA Manual of Operations (MOO).
- Implemented infrastructure for PASA2 using established resources and staff of PASA1.
- Launched two pre-clinical studies.

Year 2 Objectives in Progress

- Ongoing study procedures/experimentation being carried out for 2 animal studies
- Fund and setup new studies from RFA4a and 4b