

## **Introduction:**

The Pharmacotherapies for Alcohol and Substance Use Disorders (PASA) Consortium is funded by the Congressionally Directed Medical Research Programs (CDMRP) as part of its Alcohol and Substance Abuse Disorders Research Program (ASADRP). The PASA consortium goal is funding study applications for developing new medications that can be brought to therapeutic use to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially as related to traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). Studies of military and Veteran populations are encouraged. These medications will ideally address the comorbidity between ASUDs and posttraumatic stress disorder (PTSD), because this comorbidity is common in a military population along with mild to moderate traumatic brain injury (TBI). 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. Since both ASUD and PTSD have FDA approved pharmacotherapies, one logical starting point for treating this comorbidity might be to augment or combine these agents. The approved agents for AUD are disulfiram, acamprosate and naltrexone in either an oral and long acting injection formulation. For OUD approved agents are methadone, buprenorphine and naltrexone. For PTSD two serotonin reuptake inhibitors are FDA approved pharmacotherapies. While TBI is of interest, it has no FDA approved specific pharmacotherapies, and none of these combined disorders have FDA approved pharmacotherapies. Commercialization linked to FDA approval for these new medications or combinations of medications is critical so that early linkages to pharmaceutical companies are considered strengths of any application for PASA funding.

## **Management Core:**

The PASA Consortium is administered by a Management Core led by RTI International in collaboration with the Baylor College of Medicine (BCM). The PASA consortium leadership team consists of the Principal Investigator (PI) Rick Williams, PhD, from RTI and the co-PI Tom Kosten, MD, from BCM.

The Management Core is responsible for planning, prioritizing, and soliciting proposals, and providing oversight and coordination for future proof-of-principle basic research studies and proof-of-principle human clinical trials supported by the consortium. The Management Core will provide the administrative, protocol development and review, regulatory, statistical, resource, and data management/storage functions necessary to facilitate rapid development and accelerate translation that would perhaps not otherwise be feasible without the consortium approach. The Management Core contains multidisciplinary expertise and extensive experience in support of ASUD research. The Management Core will manage the regulatory strategy for FDA compliance leading to potential product development and licensing.

## **Research AIMS:**

The Research Roadmap for the PASA consortium calls for the solicitation of the three types of studies corresponding to our specific Aims:

1. DISCOVER novel medications and medication combinations in animal models for ASUD.

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2. Develop medications through a rational PROOF OF CONCEPT pipeline in small human studies.
3. Conduct medication safety and efficacy CLINICAL TRIALS of potential medication combinations in optimal target populations and explore functional genetic polymorphisms for matching patients to these medications.

To accomplish these Aims within the funding limitations and time frame for the consortium, we have assembled an exemplary team of experts and collaborators who will develop requests for proposals (RFPs) jointly with DoD and our pharmaceutical company partners.

Three rounds of solicitations for study applications are planned:

RFA 1: Solicitation for Discover and Proof of Concept studies. Year 1

RFA 2: Solicitation for all three types of studies. Year 2

RFA 3: Solicitation for types of studies needed to fulfill PASA goals consistent with available funding. Year 3

If there are funds available, a fourth round will be held to select additional short-duration studies. The number and type of studies selected in any round will depend on the exact number, size and type of applications submitted.

The solicitation process will consist of the following steps:

1. Short pre-applications will be submitted and reviewed by the PASA leadership. An ordered priority listing of pre-applications will be submitted to the Government Steering Committee (GSC) for final selection of pre-applicants to be invited to submit full applications.
2. Full applications will be submitted and a two-step review process will be conducted.
  - a. A scientific peer review by independent subject matter experts selected by the PASA leadership that will score each application.
  - b. A programmatic review by PASA Leadership among the top scientific scoring applications. An ordered priority listing of applications will be submitted to the GSC for final selection of applications to be funded.

**Types of Studies:**

The Aim 1 discovery studies will screen potential compounds for therapeutic potential in relevant animal models for ASUD and PTSD. During the first 2 years of PASA, we expect the greatest attention on alcohol dependence due to the availability of potential target compounds. The number of potential medications that any individual study can screen using a battery of animal testing depends somewhat on how promising the medication looks during the initial animal tests and whether a broad range of doses for that medication seems warranted. If the medication clearly makes the ASUD or PTSD models worse in early testing, then that medication should be abandoned in a collaborative decision with the GSC, PASA

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Leadership and the study PI. On the other hand, very promising medications should get more extensive testing across a broader range of doses in order to test for potential toxicities related to one or the other indication (e.g., PTSD or ASUD), as well as the range of ASUD states such as acute withdrawal vs. prevention of relapse in an abstinent state. The funded studies during the second and third rounds of solicitations will be a combination of new applications received as well as continuation studies of promising medication screening programs selected and funded during previous solicitation rounds.

The Aim 2 human proof of concept studies will take the best candidate compounds from preclinical discovery for further development. The candidate compounds could be selected from those examined as part of Aim 1 or from compounds that have previously completed similar preclinical testing. The screened compounds may include medications approved by the FDA for other indications that will be considered for repurposing to use for ASUD. This efficient re-purposing avoids the long and costly preclinical need for developing Good Manufacturing Practice (GMP) manufacturing procedures to produce the compound, Good Laboratory Practice (GLP) toxicology testing in animals, and human safety and dose ranging studies in normal subjects. After successful discovery testing for potential therapeutic effect in animal models, we can directly move re-purposed medications into our human target population of alcohol or substance abusing patients who also have PTSD and possibly TBI.

For novel compounds that do not yet have FDA approval for use in humans, two options are possible. First, we may recruit an industry partner to conduct GLP animal toxicology and GMP manufacturing and then obtain an investigational new drug (IND) application with this partner for human studies. Second, approach the National Institutes of Health for resources and funds to conduct the essential toxicology studies and manufacturing. On the other hand, if the candidate is a re-purposed medication with FDA approval for some other indication or a pharmaceutical industry compound that has an active IND and already been given to humans, then we can start testing them for medical safety and proof of concept in humans at various dosages in combination with alcohol (or the relevant drug of abuse) and for surrogate markers of potential efficacy. Surrogate markers may include substance-induced subjective effects, craving reduction, and behavioral assessments of reducing the selection of the substance in favor of monetary rewards when given these medications in combination with the abused substance. The preference for the purposes of the PASA is clearly to have compounds that are re-purposed or already have a pharmaceutical company sponsor who has an IND for use in humans.

We expect that most Aim 2 studies will take about 18 months to complete. This will consist of 4 to 6 months to plan the study (i.e., develop a full proposal, set up subcontracts, distribute study medication, develop randomization and data collection systems, and train sites); 6 months to conduct in fewer than 50 subjects using a parallel groups, within-subjects cross-over, or adaptive dose finding design that last about 1 to 6 weeks per subject depending on whether the proposal is evaluating single agents or combinations of agents; and 4 to 6 months to complete study analyses, a final clinical study report and primary study publication.

The Aim 3 efficacy clinical trials will be the most costly and time consuming of the three components of our rational pipeline, but will provide information necessary for planning future, definitive Phase III clinical trials that are required for new drug applications (NDAs) and FDA approval of our successful ASUD medications or medication combinations. The Aim 3 trials could also provide an opportunity to explore pharmacogenetics for selecting optimal patients in whom to use these medications. Such large outpatient clinical trials should take about 24 months to complete after an initial start-up study planning

period of 6 months and followed by a final analysis, report, and manuscript completion period of 6 months. While this is a very aggressive timeline for a typical multisite study, we believe this can be done with our highly experienced clinical partners from the Veterans Administration Medical Centers (VAMCs) and Military Treatment Facilities (MTFs). The major initial issue will be selecting an appropriate single medication or combination of medications for the clinical trials. Medications for these clinical trials will be selected through our rationale pipeline process for evaluating promising medications using both: (1) available data from specific Aims 1 and 2, (2) solicited study proposals, and (3) expert opinion from the GSC, our external consultants, and our internal Consortium Steering committee.

**Pharmaceutical Company Participation:**

Obtaining FDA approval for a pharmacotherapy usually is facilitated by partnership with a pharmaceutical company for the New Drug Application (NDA) filing and eventual phase 3 testing. It is recommended that such a commercial partner be obtained as early in the medication development process as possible. PASA Leadership has recruited several interested commercial partners with potential compounds to test. These partners include Lilly, Pfizer, Naurex, Indivior, Cerecor, Astellas and Alkermes. For most of their compounds, these commercial partners are considering dual indications of ASUD and PTSD.

**Study Sites:**

Studies of military and Veteran populations are encouraged. To this end, the Management Core is available to facilitate collaboration between applicants and military and Veteran medical centers.

**Number of Studies:**

The exact number and type of studies to be conducted will depend on the quantity and quality of applications received and availability of funding.

**Active Drug Studies:**

Table 1 is the list of active drug studies being conducted by the ASADRP to include both the Institute for Translational Neuroscience (ITN) and PASA consortia. Further information about the studies can be found on the ITN and PASA websites listed on the ASADRP home page.

**Research Strategy:**

Table 2 is the overall research strategy of the ASADRP that integrates both the ITN and PASA consortia and future efforts of subsequent awards. The consortia will serve as translating centers to move projects from discovery to proof of concept Phase 2 trials that seek to inform the planning of future multisite Phase 2 efficacy/dosing studies with the goal of industry handoffs in 2020 & 2023.

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**Table 1**

| <b>Drug/compound</b>    | <b>Mechanism of action</b>   | <b>Pre - clinical</b> | <b>Clinical use - proof of concept</b> |
|-------------------------|--|-----------------------|--|
| candesartan & captopril | angiotensin-1 receptor antagonist (AT1R blockers) & angiotensin converting enzyme (ACE) inhibitors | 1 study               |  |
| CERC-501                | kappa opioid antagonist  | 1 study               |  |
| NAPVSIPQ                | femtomolar-active peptide  | 1 study               |  |
| RGFP966                 | histone deacetylase (HDAC-3) inhibitor   | 1 study               |  |
| JDTiC<br>ALKS-5461      | kappa opioid antagonist  | 1 study               | Planning study                         |
| zonisamide & doxazosin  | Anticonvulsant & alpha1 alpha adrenergic antagonist  | 1 study               | 1 study                                |
| N-acetylcysteine        | modulation of glutamate and dopamine neurotransmission   | 1 study               | 2 studies                              |
| oxytocin                | human peptide hormone and neuropeptide   |                       | 2 studies                              |
| PT150                   | Glucocorticoid receptor (GR) antagonist  |                       | 1 study                                |
| tolcapone               | catechol-O-methyltransferase (COMT) inhibitor  |                       | 1 study                                |
| ASP8062                 | allosteric modulator of the gamma amino butyric acid type B (GABA-B) receptor                      | 1 study               |  |

# ASADRP Research Strategy

