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Translational Research: The Time is Now

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The National Institutes of Health (NIH) Roadmap identified the need to develop new research pathways and inter- and cross-disciplinary research teams to accelerate clinical research and solve enigmatic problems.[1] This critical need has been intensified by advances in genome science and transformational improvements in technology over the years. Whole-genome DNA sequencing of humans and model organisms is not only realistically possible and economically feasible, but it is also widespread. The opportunity has emerged to use cell and molecular techniques to decipher the "secrets of the genome" and initiate therapies based on a wide array of "omics" platforms. Breakthroughs in gene editing and gene therapy are changing the landscape of cancer, genetic, and metabolic disorders. Nonetheless, many clinicians do not yet recognize this as part of their "core business." Likewise, many basic scientists lack the clinical insights of their medical colleagues. This is due to traditional, if not parochial, disciplinary barriers. Still, for the most part, it is due to lack of knowledge and awareness of new developments in rapidly evolving scientific trajectories. Many new therapeutic options in medicine will derive from a new generation of clinical researchers having a facility with the lexicon of cell and molecular biology, genomics, next-generation sequencing, semantic data-mining, large datasets, informatics tools, and an ability to conduct extensive clinical research initiatives employing integrated, federated databases.

The past decades have been associated with changes in society and the public's interface with the healthcare system. With increasing income inequality and economic uncertainties, access to healthcare has become ever more fragmented. Disruptions in access to care and preventive services have led to a worsening of long-standing healthcare problems. In addition, racial, ethnic, socio-economic and geographic differences across our community are increasingly associated with significant health disparities. Both the opioid epidemic and the COVID-19 pandemic, while sparing no racial or ethnic group, have had a disparate impact on minority and rural populations. Notably, the effect of behavioral and mental health problems on individuals and populations' overall health has become increasingly recognized. These are challenges that affect the healthcare systems and the people in all domiciles of the United States. However, the impact of each varies by region, race, income, and historical factors. Recognition of these factors' interplay with the extraordinary breakthroughs in clinical and basic science is among the challenges faced by clinical and translational research programs. Whether it is through efforts to bring discoveries from the "bench to the bedside," to effectively testing new clinical applications, or to generalize advances to broader populations, the clinical and translational research enterprise needs to address health disparities head-on to improve health across the translational research continuum and to serve our communities.

In the previous issue of the Journal, we presented contributions from "basic science" biomedical-oriented Institutional Development Award (IDeA) programs in Rhode Island. In this issue we highlight programs for their "clinical" and "translational" impact on research and research opportunities. **ADAM CZYNSKI** et al describe studies to develop systematic approaches to the care of infants with Neonatal Opiate Withdrawal Syndrome (NOWS). **TRACI GREEN** et al provide an overview of the COBRE on Opioid and Overdoses, a collaborative research-based center addressing the opioid crisis in Rhode Island. **PETER MONTI** et al describe the Center for Addiction and Disease Risk Exacerbation (CADRE), a COBRE that is establishing a thematically linked, state-of-the-art, multidisciplinary Center investigating mechanisms whereby substance use increases risk for or exacerbates chronic disease. **SUNIL SHAW**'s overview of the COBRE for Perinatal Biology (CPB) describes their scientific focus on perinatal diseases such as preeclampsia and preterm birth, as well as more broadly on cardiopulmonary development and reproductive biology. **JEROME SANES** presents a description of the COBRE Center for Central Nervous System Function: Progress and Perspectives. **VALERIE ZABALA** has provided an overview of the Advance Clinical and Translational Research (Advance-CTR) award's efforts to bridge translational research gaps by creating a statewide hub to coordinate and leverage existing research resources and provide new career development support and funding for academic researchers, particularly junior investigators.

As we noted in our first Edition, our goals are to enhance understanding of these dynamic programs among the clinical, biomedical, and scientific research community and drive usage of the extraordinary resources that have been made available through the IDeA programs. We are fortunate to have been awarded this endowment of resources and are using them to strengthen our region's biomedical enterprise.

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The Time is NOW: Filling the Gaps in Treatment of Opioid-Exposed Infants: A Prospective, Pragmatic, Randomized Control Drug Trial

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ABSTRACT

The opioid epidemic has reached into all aspects of life in the United States. The epidemic has crossed racial, economic, social, and generational barriers. This epidemic also impacts infants. Fetal exposure to opioids can produce a withdrawal effect in newborns, referred to as Neonatal Opioid Withdrawal Syndrome (NOWS). NOWS treatment lacks a standard approach, with prominent variation across the United States. Furthermore, many treatment strategies for NOWS are not evidence-based but reflect anecdotal experience. Variable approaches to NOWS treatment contribute to more extended hospital stays and greater postnatal opioid exposure. The most prolonged period of NOWS treatment occurs during the weaning phase. This paper describes the first prospective randomized control trial to address systematized weaning of opioids for infants with NOWS.

KEYWORDS: Neonatal Opioid Withdrawal Syndrome, Neonatal Abstinence Syndrome, Substance Use Disorder, Opioids

INTRODUCTION

The opioid epidemic in the United States has affected all aspects of our society, including pregnant patients and their newborns. The incidence of maternal opioid use in the United States has increased substantially since 2000,[1] affecting both rural and urban communities.[2] The rise in opioid use is not just in illicit substances, but in prescription opioids, and a subsequent surge in medication-assisted treatment.[3] The increased incidence of opioid use in pregnancy has contributed to an increase in Neonatal Opioid Withdrawal Syndrome (NOWS), the clinical syndrome that reflects the signs of opioid withdrawal in newborns. The National Institutes of Health (NIH) has developed an aggressive research strategy to make headway in the epidemic under the initiative's umbrella, Helping to End Addiction Long-Term (HEAL).[4] HEAL is a trans-agency national initiative to address the opioid public health crisis. In 2019, the Health Care Cost and Utilization Project by the Agency for Healthcare Research and Quality (AHRQ)[5,6] reported rates of NOWS from < 3.2 to > 10.9 newborns per 1000 births. NOWS rates vary by region within the United States.[2] The rates are particularly high across the Northeast and the Appalachian states. The states most affected are West Virginia, Vermont, and Kentucky, where rates are 48.1, 28.0, and 22.9 per 1000 live births.[2] While NOWS initial focus was on newborn hospitalization, there is now growing recognition that NOWS effects extend beyond the neonatal period and impact developmental outcomes.[7,8] Also, infants with NOWS have increased hospital readmission rates than infants without opioid exposure (46.3/1000 vs. 25.6/1000 live births in 2016.[9] Hospital readmission reflects higher rates of failure to thrive, seizures, and child abuse. This article will focus on the neonatal aspects of opioid withdrawal to identify gaps in treatment approaches and a recently initiated clinical trial to fill these gaps.

BACKGROUND

A recent Journal of Pediatrics editorial emphasized the rapid rise of NOWS in the United States. It provided a framework to target research initiatives and care delivery innovations for these infants.[10] Research and quality improvement initiatives should be safe, effective, patient-centered, equitable, and achieve the goals of limiting ongoing infant opioid exposure, minimizing family separation, and reducing healthcare expenditures. To date, there is a lack of randomized clinical trials that rigorously evaluate aspects of NOWS treatment.[11]

Quality improvement (QI) methods to standardize NOWS treatment have been successful in reducing the length of therapy (LOT) and hospital stays among affected infants.[12,13] There is the acceptance that initial care should be individualized, supportive and non-pharmacologic. This has been the focus of many QI initiatives.[3] These measures include minimizing environmental stimuli,[14] encouraging breastfeeding, and providing on-demand nutrition. If non-pharmacologic strategies cannot control NOWS signs, pharmacological therapy is indicated. The pharmacological treatment uses opioid replacement to control NOWS signs to avoid severe central nervous system dysfunction. In contrast to QI initiatives addressing non-pharmacologic strategies, limited randomized clinical trials guide NOWS pharmacologic treatment.

Pharmacologic treatment traditionally begins once an infant has reached a predetermined threshold using a NOWS

assessment tool. There are many different NOWS assessment tools; the original and gold standard is the Finnegan Neonatal Abstinence Scoring System (FNASS).[15] Irrespective of the assessment tool, once a child crosses the treatment threshold, opioid replacement therapy (ORT) occurs in three phases: initiation, stabilization, and weaning. Initiation is the start of ORT, stabilization is the interval of time where no further escalations in dose are needed, and weaning consists of serial reductions in ORT and/or lengthening the time interval between doses.

Medical professionals generally agree on ORT phases, but they do not agree on a standard of care for pharmacologic treatment of NOWS.[16] Clinical teams may use different drugs as first-line agents (morphine, methadone, or buprenorphine) and second-line agents (phenobarbital or clonidine), with limited data to guide either. To date, there have been five trials that have enrolled a total of 345 infants.[12-16] Three trials were terminated early due to slow recruitment.[17-19] These trials compared morphine to another medication for NOWS treatment (phenobarbital, methadone, or buprenorphine). The inclusion of morphine in each arm reflects that morphine has been used most widely for ORT. This was further supported by data from the ACT NOWS Current Experience, a retrospective chart review conducted among the IDeA States Pediatric Clinical Trials Network (ISPCTN) and Neonatal Research Network (NRN) indicated that morphine was the first-line drug for ORT in 86% of NOWS infants and represented one of the few aspects of care without variation.[20] The ACT NOWS Current experience data affirms the historical use of morphine and reflects limited high-quality data to effect change in treatment.

Of the three phases of opioid replacement therapy, the weaning phase is the longest and contributes to the greatest variation on length of hospitalization. Like other aspects of NOWS care, there is no standardized approach to weaning ORT. A review of practice guidelines from over 20 centers in the ISPCTN and NRN affirm the weaning decrements' variability. Centers most often wean ORT by a percentage reduction of the stabilization dose, varying from 10% to 15%; some centers even reduce by 20%. Although a standard of care for weaning morphine does not exist, the plurality of existing clinical trials used 10% reductions of the stabilizing dose.[17-19,21,22] The interval between dosage weans also varies by center and ranges from every 12 to 48 hours. This facet of weaning was absent from the prior trials and remained a significant gap in previous studies' interpretation.

The weaning phase of ORT has the greatest variation and thus shortening the weaning phase has the greatest potential to impact healthcare costs. Based on data from the ACT NOWS Current Experience, the average LOS for pharmacologically treated infants is 14.6 days. A treatment reduction of 2.0 days represents a14% reduction in treatment duration and has the potential to reduce healthcare costs by more than $15.7 million per year. Potential cost savings would be even greater for hospitals that care for NOWS infants in NICUs or special care nurseries. Unfortunately, there are no randomized trials to inform clinicians of potentially better regimens to wean morphine or methadone.

OPPORTUNITY FOR AN INTERVENTION

The absence of a well-studied weaning strategy contributes to wide practice variation adding to LOS and costs. Since clinical teams want to minimize NOWS signs' recurrence as drug treatment is reduced, and a state of inertia is often perpetuated whereby clinical consensus drives decisions rather than an evidence-based protocol. It is easy for clinical teams to adopt a "let's wait another day" mentality. Given the potential to reduce healthcare costs with a systematic weaning strategy, investigators at Women & Infants Hospital of Rhode Island are leading a large multicenter randomized trial to develop an evidence-based weaning strategy. The trial's hypothesis is that among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for NOWS, a rapid-wean intervention (15% reduction from stabilization dose) will reduce the days of opioid therapy from the first weaning dose to the cessation of opioid, compared to a slow-wean intervention (10% reduction from stabilization dose). This trial will be a pragmatic, randomized, blinded trial. It will compare what is used by most centers (10% decrements from the stabilization dose) with an emerging practice of faster weaning (15% decrements from the stabilization dose). The following is an overview of this clinical trial's essential elements, which began recruitment in September of 2020.

INCLUSION CRITERIA

The study has both site-level and patient-level inclusion and exclusion criteria. Site- inclusion criteria are that the hospital provides pharmacologic treatment to at least 12 opioid-exposed infants each year, uses a scoring system to assess for signs of NOWS, and the primary opioid replacement therapy is either morphine or methadone. Site-level exclusion criteria are discharging more than 10% of infants from the hospital on opioid replacement therapy.

Infant-level inclusion criteria are gestational age $\geq$ 36 weeks, receiving scheduled pharmacological therapy with morphine or methadone as the primary drug treatment for NOWS secondary to maternal opioid use, and tolerating enteral feeds and medications by mouth. Infant-level exclusion criteria are major birth defects, surgery, hypoxic-ischemic encephalopathy, seizures, treatment with opioids for reasons other than NOWS, respiratory support greater than 72 hours, use of other opioids for NOWS, and/or weaning before randomization.

PRAGMATIC FEATURES

This is a pragmatic, randomized, blinded trial of opioid weaning; **Figure 1** illustrates when the study interventions will occur during the hospitalization.

The treatment of NOWS has regional, state, and center differences. With such variation, this trial purposely incorporated pragmatic components into the design. A practical design's benefits are to gain acceptance among participating centers and allow center-specific management practices for NOWS treatment after birth and before randomization. The protocol-directed elements are limited to direct care management after randomization during the weaning phase. Pragmatic features may include the following practices:

- Location of care for the infant (mother-baby unit, Neonatal Intensive Care Unit (NICU) or Pediatric floor, etc.).
- Monitoring frequency of vital signs and the use of cardiopulmonary monitors.
- Agreement to optimize non-pharmacologic treatment based on choice from a protocol-provided standardized bundle.
- Use of breast milk and breastfeeding.
- Scoring assessments of NOWS signs.
- Scoring criteria to initiate ORT and thresholds for weaning vs. escalation of study drug.
- Choice of opioid (morphine or methadone) as the primary treatment and dosing to initiate pharmacological therapy.
- Initiation and dosing adjustment of the second- and third-line drugs for NOWS signs (e.g., phenobarbital, clonidine) if NOWS signs are not adequately controlled with ORT.
- Duration of stabilization whereby the clinical team determines the interval over which no further drug dosage changes are needed to control NOWS signs before weaning is initiated.

The pragmatic components will hopefully bolster recruitment and center engagement. To account for the pragmatic elements in the data analysis, randomization will be stratified by center.

STUDY INTERVENTION

Infants will be randomized to either a rapid-wean intervention arm (15% reduction from stabilization) or a slow-wean intervention arm (10% reduction from stabilization) whenever the clinical team weans the opioid (**Figure 2; Table 1**). The clinical team will discontinue ORT when the infant can tolerate 25% or 20% of the stabilization dose without NOWS signs in the rapid- and slow-wean arms, respectively.

There are eight weans or dose levels for the rapid- and slow-wean intervention arms, each representing the amount of opioid the clinical team will administer. Infants in the rapid-wean intervention arm will undergo 5 study drug weans followed by three placebo levels. Infants in the slow-wean

Figure 1. Timing of Study Intervention in Relationship to Hospital Stay

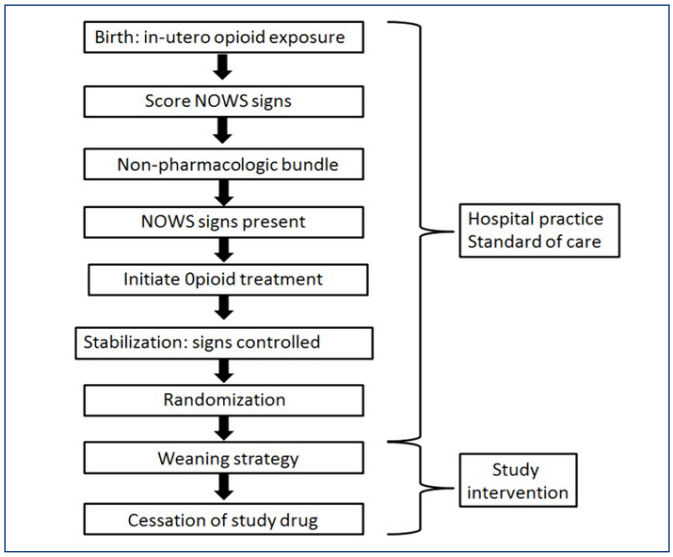


Figure 2. Overview of the Study Intervention

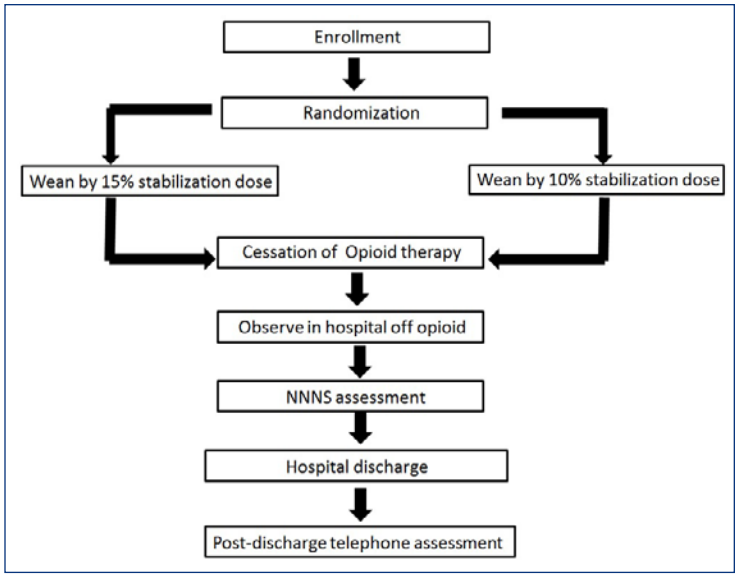


Table 1. Dose Levels of the Rapid-Wean and Slow-Wean Interventions

Dose	Rapid wean: 15% of stabilization dose	Slow wean: 10% of stabilization dose
Stabilization Dose	100%	100%
Dose Level A	85%	90%
Dose Level B	70%	80%
Dose Level C	55%	70%
Dose Level D	40%	60%
Dose Level E	25%	50%
Dose Level F	Placebo	40%
Dose Level G	Placebo	30%
Dose Level H	Placebo	20%

arm will undergo 8 study drug steps and no placebo levels. The rapid-wean intervention arm requires three placebo levels to maintain the blind. If opioid escalation does not occur, the infant will receive eight dose levels over 8 study days. However, if there are escalations, the clinical team will need to repeat the prior higher dose level (escalation), and there will be eight dose levels but more than 8 study days.

The trial has specific elements that centers must declare as part of the weaning intervention. Centers can choose which opioid, morphine, or methadone they plan to administer and at which frequency. Centers that choose morphine will need to select a dosing frequency of either every 3 hours or every 4 hours. Centers that choose methadone will need to select a dosing frequency of either 8 or 12 hours.

The clinical team will use hospital-specific assessment tools to determine the severity of NOWS signs, and infants with NOWS will be scored with these tools every 3 to 4 hours. Based on the assessment scores and as directed by center practices, infants who reach a threshold for escalation during the weaning phase will resume the previous dose level. To avoid the inertia among clinical centers when weaning drug ORT, centers will need to either wean or escalate every 24 hours. Centers are free to wean more rapidly and can escalate before 24 hours if center guideline criteria are met. Should a patient not reach center thresholds for escalation, the protocol will direct them to wean the infant. In situations where an infant is approaching the end of 24 hours and the team is concerned by a pattern of scores, the clinical team can monitor the infant beyond the 24-hour window until the concerning pattern dictates an escalation or a wean. This extended period can continue for 12 hours before it meets the criteria for a protocol violation. Hospitals do not need to use the entire 12-hour period to either wean or escalate if the infant completes the requirements before 12 hours.

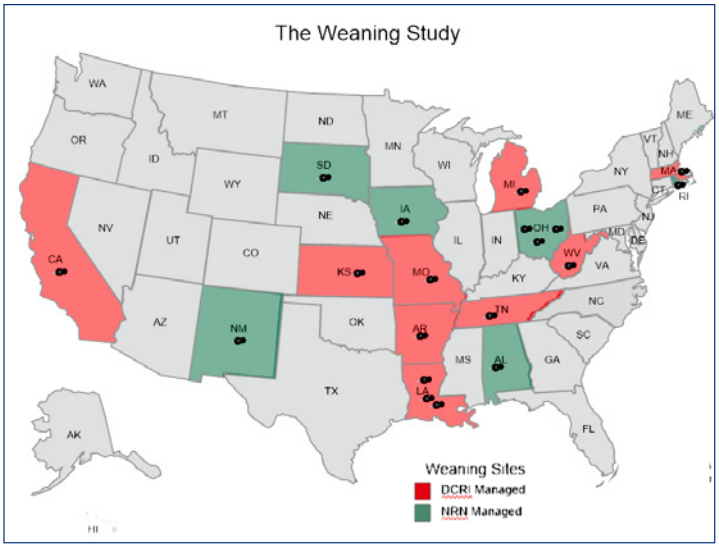
STUDY OUTCOME

This study has a single primary outcome and multiple secondary outcomes. The primary outcome will be the number of days of opioid treatment (used as primary treatment), including escalation, resumption, and spot treatment, from the first weaning dose to opioid cessation. The primary outcome will be assessed by analyzing data from all infants undergoing rapid-wean compared to slow-wean with morphine or methadone. Days of opioid treatment is a single outcome that will be a function of a) the weaning algorithm and b) the extent of recurrence of NOWS signs. The use of hospital guidelines combined with study protocol guidelines will ensure that NOWS signs deemed clinically meaningful result in appropriate treatment of the infant. The trial's secondary outcomes will focus on 1) additional measures of efficacy, 2) safety, and 3) 18 months follow-up.

STATISTICAL ANALYSIS PLAN PRIMARY OUTCOME

This is an intention-to-treat trial, and the outcome of the primary hypothesis will determine intervention differences of two means by analyzing the average number of days of opioid treatment from the first weaning dose to the cessation of opioid therapy. The study is powered to enroll 502 infants with 251 infants to each arm, irrespective of the proportion of infants treated with morphine or methadone. The projected recruitment window is 3.3 years, with 25 centers enrolling. At present, 20 centers are participating, and additional centers are being evaluated for participation (**Figure 3**).

Figure 3. Map of ISPCTN, NRN, and Other Sites



CONCLUSION

When non-pharmacological therapy is inadequate to control NOWS signs, pharmacologic treatment is used. Unfortunately, there are heterogeneous practices in all aspects of pharmacological therapy. This proposed study is a pragmatic trial powered to detect a two-day difference in the LOT between a rapid- and a slow-wean intervention. Hospitals will be able to use either morphine or methadone with the knowledge that we may find a positive treatment effect for both, one, or neither drug. The speed that infants can be successfully weaned without recurrence of NOWS signs is unknown. If successful, this clinical trial will limit ongoing opioid exposure for infants, minimize separation of the family, and reduce healthcare expenditures.

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COBRE on Opioid and Overdose: A Collaborative Research-Based Center Addressing the Crises in Rhode Island and Beyond

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ABSTRACT

Overdose deaths across the country have spiked since the onset of the COVID-19 pandemic. It is crucial now, more than ever, to address the continuing and worsening, complex and dynamic opioid and overdose epidemics. In 2018, The Center of Biomedical Research Excellence (COBRE) on Opioids and Overdose, based at Rhode Island Hospital, launched with three major goals: 1) establish a center of scientific excellence on opioids and overdose; 2) train the next generation of scientists to become independent investigators and address the opioid and overdose crises; and 3) contribute to the scientific progress and solutions to combat these epidemics. To date, we have made substantial progress. While the opioid and overdose crises continue to evolve, the COBRE on Opioid and Overdose and its team of investigators are well poised to address the daunting task of understanding and meaningfully addressing these deadly epidemics, with the ultimate goal of saving lives.

KEYWORDS: opioid, overdose, fentanyl, prison, jail

INTRODUCTION

Preliminary data from 2020 suggests that there has been a 30% increase in overdose deaths in Rhode Island. Despite a gradual decline in overdose deaths over the prior four years, 2020 marks, by far, the worst year yet.[1,2] This alarming trend is not unique to Rhode Island. Overdose deaths across the country have spiked since the onset of the COVID-19 pandemic.[3] The horror of the pandemic has diverted attention away from the worsening overdose crisis, which was the leading cause of accidental death nationally before the pandemic. It is crucial now, more than ever, to address the continuing and worsening opioid and overdose epidemics. One thing is quite clear – the opioid and overdose epidemics are very complex and dynamic and demand extensive attention to address them effectively.

A majority of the overdose deaths in the country are opioid-related.[5] The current opioid epidemic in the United States started in the mid-1990s when pharmaceutical companies began heavily marketing their opioid medications to physicians eager for pain management solutions.[6] The first wave of the opioid crisis in the United States was defined by physicians over-prescribing opioids and was marked with a steady increase in overdose deaths.[7] By 2010, the prescription opioid crisis had evolved into an illicit heroin epidemic as opioid dependence became more common, resulting in higher demand for a more consistent pill supply than was affordable or accessible.[8] The impact of increased demand for heroin has most recently led to increased production of more powerful synthetic opioids, notably fentanyl and its related analogs. Illicit fentanyl and synthetic compounds are between 50 and 100 times more potent than heroin and have a more rapid onset of action, making them far more deadly for people without adequate tolerance or unintentionally consuming fentanyl,[9] for example, when it contaminated cocaine. In 2018, over 70% of Rhode Island's 308 overdose deaths involved fentanyl.[5] Further, with increases in fentanyl presence in the illicit drug supply and increases in polysubstance use in Rhode Island, there has also been a recent surge in overdoses involving stimulants (e.g., cocaine and methamphetamine) alone and together with opioids,[5] underscoring the need for interdisciplinary research and programming to address the opioid and overdose epidemics.

THE COBRE ON OPIOIDS AND OVERDOSE

In 2018, The Center of Biomedical Research Excellence (COBRE) on Opioids and Overdose launched with three major goals: 1) establish a center of scientific excellence on opioids and overdose; 2) train the next generation of scientists to become independent investigators and address the opioid and overdose crises; and 3) contribute to the scientific progress and solutions to combat these epidemics. To date, we have made progress on all three fronts.

The COBRE on Opioids and Overdose, based at Rhode Island Hospital (RIH), is the first center of its kind to address the opioid and overdose epidemics collaboratively. The center is funded with a five-year, Phase 1 grant from the National Institute of General Medical Sciences (NIGMS) and is currently in its third year (P20GM125507). The COBRE is an innovative, multidisciplinary research center that brings together dedicated investigators and utilizes a comprehensive approach to understand and develop solutions to the opioid and overdose crises. There is a tremendous need, especially considering the COVID-19 pandemic, for a greater scientific understanding of the mechanisms underpinning opioid use disorder and overdose and developing effective interventions to address them.

Structures and Cores

The COBRE's director Josiah Rich, MD, MPH, and deputy director Traci C. Green, PhD, MSc, are both expert advisors to the Governor's Overdose Prevention and Intervention Task Force with over 40 years of combined research experience on people with opioid use disorder and other substance use disorders. Over the past two years, they have spearheaded the Center's mission to bring together experts from across the state to provide mentorship to junior investigators committed to addressing the opioid epidemic that is devastating Rhode Island. The COBRE's External Advisory Committee, NIGMS, and RIH have provided an open and encouraging environment that has allowed the Center to fund new, creative and innovative ways to address the epidemic by partnering with local organizations such as the Rhode Island Communities for Addiction Recovery Efforts (RICARES), the Rhode Island School of Design (RISD) and the Providence/Boston Center for AIDS Research (CFAR).

Within short order, the COBRE on Opioids and Overdose has proven to be extraordinarily successful. Since its inception in 2018, it has supported over 35 Investigators, 9 Pilot Projects, 4 Research Projects, and 3 Research 'Cores' (see **Table 1**). Additionally, 40 publications have received COBRE support, 21 of which have been published by COBRE Junior Investigators, Pilot Project Awardees, and COBRE Graduates; 22 scientific presentations have been given, and 16 applications have been submitted for funding outside the COBRE funding mechanism. Additionally, two Research Project Leaders have graduated from the COBRE and received independent funding. The COBRE on Opioids and Overdose has worked exceptionally hard to establish a presence in Rhode Island and beyond through cutting-edge research and innovative projects showcased on the COBRE website, along with a successful 2020, week-long, virtual symposium jointly hosted with the University of Nebraska's Rural Drug Addiction Research COBRE Center and the West Virginia Clinical and Translational Science Institute with over 400 attendees. Social media posts and YouTube channel platforms are further leveraged to amplify the COBRE reach and elevate the contributions to science and community through short, engaging videos.

Table 1. COBRE on Opioids and Overdose Research Projects and Pilot Projects

Research Project	Neonatal Abstinence Syndrome (NAS): Fetus to First Years	Adam Czynski, DO	9/1/18–present
Research Project	CoMBAT Opioid Use Disorder: A Pilot RCT of a Combined Medication and Behavioral Activation Treatment for People Living with Opioid use Disorder	Jaclyn White Hughto, PhD, MPH	5/1/19–present
Research Project (proposed)	Estimating the Causal Effects of Residential Eviction on Substance Use Treatment Outcomes	William C. Goedel, PhD	3/1/21–present
Pilot Project	Unintentional Fatal Opioid Overdose in Women: Toxicologic and Pharmacologic Sex Differences in Cause of Death	Rachel S. Wightman, MD	11/1/20–present
Pilot Project	Evaluation of a Nonopioid Recovery Pathway After Percutaneous Nephrolithotomy	David Sobel, MD	12/1/20–present
Pilot Project	Trauma and Stressor-Related Disorders Among Layperson Opioid Overdose Responders	Brendan Jacka, PhD	12/1/20–present
Pilot Project	Buprenorphine with Additional Rx Exposure (B-WARE)	Steven Kogut, PhD	12/1/20–present
Pilot Project	Development of a Text Message Delivered Intervention to Promote Engagement in Medication Assisted Treatment among the Criminal Justice-Involved Population	Kirsten Langdon, PhD	4/1/20–present
Pilot Project	Co-Occurrence of Post-traumatic Stress Disorder and Opioid Use Outcomes among Community Individuals	Nicole Weiss, PhD	12/1/19–present
Mini-Pilot Project	Factors Associated with Establishment of Emergency Department-Initiated Buprenorphine Induction for Opioid Use Disorder in Rural New England.	Noah Rosenberg, MD	1/16/20–1/15/21
Graduate–Research Project	Informed Opioid Prescribing for Acute Musculoskeletal Pain After Motor Vehicle Collision: A Support Tool for Assessing Risks and Benefits of Analgesic Medications Before Prescribing (STAAMP).	Francesca Beaudoin, PhD, MD	9/1/18- 2/28/20
Graduate–Research Project	Contingency Management in Combination with MAT for Opioid Use Disorder	Sara Becker, PhD	9/1/18–11/14/18
Former Pilot Project Awardee	Use of Non-opioid and Non-drug Treatments for Chronic Pain: Trends and Relationship with Opioid Prescribing and Outcomes in the Rhode Island All Payer Claims Database	Patience Moyo, PhD	1/1/19–12/31/20
Former Pilot Project Awardee	Monitoring Newborn Sleep to Improve Treatment and Outcomes from Opioid Exposure	Amy Salisbury, PhD	3/1/20–7/1/20

Administrative Core

The COBRE is led by an Administrative Core with an oversight structure and has three scientific Cores to support Rhode Island-based investigators. This Administrative Core, responsible for the general management of the COBRE, oversees three committees (Executive Committee, Internal Advisory Committee, and External Advisory Committee) that provide integral feedback on the center's progress and ensure the program is meeting the guidelines and missions of NIH, NIGMS, RIH, and the COBRE. The Executive Committee plays an essential role in monitoring the COBRE's Research Cores' productivity and finances and facilitates additional mentorship for the Research and Pilot Project Leaders. The Internal Advisory Committee provides feedback specifically on COBRE projects' development and provides mentorship to junior investigators. Lastly, the External Advisory Committee conducts an annual evaluation on the progress of the Project Leaders, the mentorship program's effectiveness, and the usefulness of the Core services. The External Advisory Committee's Year 2 annual evaluation was overwhelmingly positive and stated that they "were highly impressed with the progress the investigators are making and how successful they have been in publishing and writing grants." In addition to overseeing these feedback-providing committees, the Administrative Core also leads several working groups, including the Medication for Opioid Use Disorder in Corrections Working Group. This working group is in the process of developing a comprehensive website that streamlines up-to-date data on medication for opioid use disorder in correctional settings nationally (see The Prison Opioid Project on www.opioidcobre.org). In addition to the Administrative Core, the three research 'Cores' collaborate closely and play an essential role in supporting Rhode Island-based investigators with services that assist them in refining research methods, increase their network of collaborators, assist with grant and manuscript development and provide additional resources as needed.

Data and Research Methods (DRM) Core

The Data and Research Methods (DRM) Core, led by Dr. Brandon Marshall at Brown University's School of Public Health, assists COBRE Project Leaders and Pilot Project Investigators with methodological, analytic, and data-related support. This Core has focused on supporting junior investigators and pilot applicants during the past two years by providing workshops on innovative research methods. The DRM Core has done a remarkable job supporting junior investigators by reviewing and assisting in analytical plans revisions. Additionally, the DRM Core has also organized and hosted a series of talks focused on innovative research and methods, as well as co-sponsored a Community Overdose Data Workshop with the Brown School of Public Health that focused on using novel analytic methods, such as machine learning and predictive analytics, to better implement interventions to prevent fatal overdoses. Notably, the DRM Core has provided analytic support for the publication of seven new manuscripts published in prestigious journals, including The Lancet and Addiction.

Special Populations (SP) Core

The Special Populations (SP) Core, led by Drs. Curt Beckwith and Tim Flanigan located at The Miriam Hospital, supports investigators and researchers in addressing practical challenges posed when conducting opioid and overdose research with vulnerable and underserved populations. This Core supports the COBRE's mission by building an infrastructure to recruit and retain vulnerable individuals as participants in research studies, build capacity in the ethical conduct of research, and promote research among populations most impacted by opioids and overdose. The SP Core has provided mentorship on research protocol design, study development, institutional review board applications, and study recruitment materials. The SP Core also works to develop training modules (seminars, webinars, and course curriculum) to promote clinical and translational research among populations most impacted by opioids and overdose. Notably, the SP Core recently created a multi-disciplinary continuing education harm reduction module targeting community health providers.

The SP Core has successfully established a Community Advisory Board (CAB). The CAB was developed and expanded by reaching out to community partners to identify individuals interested in bettering overdose-related research. Through these efforts, the CAB successfully recruited 42 members throughout the five initial meetings. Members of the CAB include people who are in recovery from opioid use disorder; people living with HIV; people who are homeless; people with a history of incarceration; people who use drugs; people with a history of sex work; recovery and harm reduction advocates; and people of diverse gender identities, races and ethnicities, sexual orientation, and ages. The CAB diversity is essential to the Core's work to support investigators in researching vulnerable populations. The CAB is committed to ensuring low-barrier access to the meetings and partners with recovery and harm reduction specialists to determine meeting locations. Additionally, transportation and meals are provided at every meeting. The CAB meetings have addressed a spectrum of concerns and community needs, from initial discussions around the role of CABs in supporting research to reviewing intervention content to providing feedback to Junior Investigators on their methods such as recruitment and reimbursement. A discussion-based CAB meeting about stigma and discrimination, facilitated by a community member, helped the SP Core identify the need for further research and developed a call for pilot programs specifically focused on the impact of stigma on recovery.

Translational and Transformative Research (T2) Core

The Translational and Transformative Research (T2) Core led by Drs. Traci C. Green and Susan Ramsey is dedicated to providing expert support in translating innovative findings to transform the care of addiction and overdose. The urgency of the opioid crisis in our state calls for innovative research and interventions and necessitates rapid dissemination of said research. The goal of the T2 Core is to establish a hub of translational and transformative resources to support junior investigators as they bridge research from theory and bench to bedside, from bedside to neighborhood, and from the community to policy change, to transform the care of opioid use disorder and the prevention of overdose. Due to the challenges posed by COVID-19, the T2 Core met with investigators. It helped them revise their protocols to maximize productivity, minimize study delays, and continue to pursue the aims of the studies. Additionally, the COBRE recently partnered with RIH to establish a buprenorphine hotline that can be used to access low barrier buprenorphine during the pandemic. To increase the hotline's reach, the T2 Core assisted in the development and distribution of materials regarding the hotline in the community. In addition, T2 Core members have engaged in community outreach activities to increase hotline traffic, including placing phone calls to patients who have been recently seen in local emergency departments for an opioid-related cause.

In fall 2019, the T2 Core hosted a successful Hackathon event. Teams of community members, students, and professionals were charged with developing innovative "hacks" or solutions to combat the opioid epidemic. The participants were encouraged to collaborate to address one or more topics: a community strategy for opioid overdose, healthcare solutions to opioid overdose, or policy solutions to opioid overdose. The three winning teams created high impact projects that continue to garner community and professional development opportunities (see YouTube Channel on www.opioidcobre.org). As a result of the hackathon, these projects received COBRE funding and became feasibility projects under the COBRE to further develop their innovations.

The COBRE on Opioids and Overdoses is not only committed to mentorship and collaboration among its investigators, but it also has been dedicated to institutional and organizational partnerships. In September 2019, the COBRE on Opioids and Overdose and the Rural Drug Addiction Research (RDAR) COBRE at the University of Nebraska – Lincoln began small efforts to collaborate to increase access to research around substance use and addiction science more broadly. This started with brief phone calls between center PIs and administrators, a site visit and quickly expanded to a fully realized partnership as synergies emerged across almost all programming areas. Our early goal of sharing more information across centers has grown into a valuable collaboration that includes hosting joint seminars, events, workshops, training, and conference symposiums. We built on the existing resources and expertise that each of our COBREs provides to further increase our efficiencies and capacities at both institutions. This successful collaboration with the RDAR COBRE has piloted efforts to grow our successful COBRE collaboration with other substance use focused centers across the US in the coming years.

CONCLUSION

Although Rhode Island is the smallest state, it has been disproportionally impacted by the opioid and overdose crises. However, it has made a substantial impact. In 2017, the state government initiated the Governor Raimondo's Overdose Prevention and Intervention Task Force. Three COBRE Leaders serve as the Task Force's Expert Advisors. Additionally, the Rhode Island Department of Corrections initiated the first-ever statewide comprehensive program for medication for opioid use disorder in a correctional setting. This program has led the charge to provide people who are incarcerated access to the gold-standard treatment for opioid use disorder in a correctional setting. While the opioid and overdose crises continue to evolve, the COBRE on Opioid and Overdose and its team of investigators are well poised to address the daunting task of understanding and meaningfully to address these deadly epidemics to save lives.

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Disclaimer

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Brown University COBRE Center for Addiction and Disease Risk Exacerbation

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ABSTRACT

The Center for Addiction and Disease Risk Exacerbation (CADRE) is a COBRE establishing a thematically linked, state-of-the-art, multidisciplinary Center investigating mechanisms where-by substance use (SU) increases the risk for or exacerbates chronic disease. It does so by employing a combination of behavioral and physiological laboratory-based approaches across several substances and across several diseases. COBRE projects investigate mechanisms underlying effects of opioids, cannabis, tobacco, and alcohol on risks for and progression of SU-related disease. Though linkages between SU and disease are well documented, physiological mechanisms underlying such associations are poorly understood, mainly because published studies use cross-sectional designs that do not allow for causal interpretations. Mechanisms studied in CADRE projects include systemic inflammation, immune system dysregulation, high blood pressure, pulmonary effects, and carcinogen exposure. A Clinical Laboratory Core provides infrastructure, resources, and scientific expertise and a center-wide database of risk factors associated with the development of SU and chronic disease.

KEYWORDS: substance use, chronic disease, mechanisms, interdisciplinary, early career faculty

INTRODUCTION

The Brown University Center for Alcohol and Addiction Studies has established the Center for Addiction and Disease Risk Exacerbation (CADRE), a COBRE funded by the National Institute of General Medical Sciences (NIGMS) in August 2019. The CADRE is led by Peter M. Monti, PhD, Director of the Brown University Center for Alcohol and Addiction Studies and Professor of Behavioral and Social Sciences (BSS), by Jasjit S. Ahluwalia, MD, Professor of BSS and Professor of Medicine, and by Jennifer W. Tidey, PhD, Professor of BSS and Associate Dean for Research at the Brown School of Public Health. Together these three constitute the CADRE's Executive Committee, which has the formal charge of internal governance of the Center.

The primary goal of this Center is to establish a thematically linked, state-of-the-art, multi-disciplinary center to investigate the mechanisms by which substance use increases the risk for or exacerbates chronic disease. More specifically, our CADRE investigates the biobehavioral mechanisms whereby substance use impacts disease. It does so by employing a combination of behavioral and physiological laboratory-based approaches and across several substances of abuse and several chronic diseases. Our overarching goal in establishing this Center is to create a vehicle that will support the emerging careers of promising early-career interdisciplinary faculty, and in so doing, enhance their competitiveness for external independent funding. The ultimate goal is to improve the lives of those living with substance use disorders (SUDs).

ASSOCIATIONS BETWEEN SUBSTANCE USE AND MAJOR MEDICAL ILLNESSES

Substance use negatively affects the risk, management, progression, and outcomes of chronic disease and contributes to socio-economic and racial/ethnic disparities. Prevalence rates of medical conditions among patients with versus those without SUDs support this thesis. Furthermore, risks of disease or disease progression are exacerbated among those otherwise at risk or who already have chronic medical conditions, such as people living with HIV (PLWH) and people living with chronic pain.[1-3] For example, among sexual minority men who have sex with men, alcohol contributes to the fact that they are more severely affected by HIV than any other group in the United States. Further, among HIV-positive smokers, tobacco accounts for more deaths than HIV.

Though linkages between substance use and disease are well documented, physiological mechanisms underlying such associations are poorly understood and underappreciated, mainly because the literature is based on studies that use cross-sectional designs that do not allow for causal interpretations. For example, as pointed out by Bahorik and colleagues,[4] documented relationships between pain and illicit opioid use may evolve because patients who are prescribed pain medication later migrate to illicit opioid use, or patients misuse illicit opioids instead of using pain medications, or both. Studies using experimental designs are needed to understand the biobehavioral mechanisms that link substance use and chronic disease and inform the development of

targeted prevention and intervention efforts to reduce risks.

Unfortunately, experimental research in this area is relatively nascent. A review by Bachi et al[5] characterizes the effects of SUDs on the organism as "accelerated aging", which occurs when biological aging (i.e., wear and tear on one's organs) outpaces chronological age. Factors by which SUDs contribute to accelerated aging include effects of drugs on the brain (brain dopamine, cerebrovascular pathology, neuroinflammation, enhanced stress sensitivity), other physiological effects of drugs (on cardiovascular, pulmonary, metabolic, immune, and circadian health), and effects of drugs on behavior and social functioning (poor nutrition, poor sleep patterns, lack of physical activity, stigmatization, impaired access to healthcare, low family/community support, poverty, infectious diseases and involvement in the criminal justice system).[5]

Clearly, this is a vast area of research. Fortunately, pathophysiological processes underlying these factors are beginning to be identified. One major pathway is the promotion of oxidative stress by drugs and alcohol, leading to cellular damage, tissue injury, and inflammation. Exposure to toxic substances promotes inflammation in the gut, liver, brain, and other organs. Inflammation in combination with increased oxidation may be especially damaging.[6] Oxidation, inflammation and stress hormone exposure also accelerate telomere shortening[7] and stem cell decline,[8] diminishing resilience and regeneration capacity. When chronically present, oxidative stress and inflammation lead to pathologies such as diabetes, cancer, cardiovascular disease, and neurodegenerative diseases.[9]

A basic tenant of the CADRE is that investigating systems and pathways involved in associations between substance use and chronic disease, and intervening to prevent these associations, requires multidisciplinary, multilevel approaches, which bring together behavioral scientists, clinical researchers, physicians, and basic scientists who conduct basic biology, prevention and intervention studies, as well as lab-based human behavioral studies. CADRE studies are especially attentive to the many biological and socio-environmental factors that contribute to racial and ethnic disparities. Our interdisciplinary multilevel approach, focused on related questions using shared resources and learning experiences, not only is poised to contribute new knowledge but importantly serves as the nexus and path toward independence for the next generation of CADRE scientists. The research projects and pilot studies comprising our CADRE investigate mechanisms underlying the effects of opioids, cannabis, tobacco, and alcohol on risks for SUD-related disease progression. Mechanisms studied in the initially funded four CADRE research projects include systemic inflammation, immune system dysregulation, high blood pressure, pulmonary effects, and carcinogen exposure. CADRE studies are serviced by an Administrative Core and a Clinical Laboratory Core.

ADMINISTRATIVE CORE

Peter M. Monti, PhD, CADRE PI, is Brown University's Distinguished Professor of Alcohol and Addiction Studies and Director of the Center for Alcohol and Addiction Studies (CAAS). He founded and is currently Deputy Director of Brown University's Alcohol Research Center on HIV and is PI of CAAS's Alcohol T32 Postdoctoral Training Program. His research interests span understanding the biobehavioral mechanisms involved in behavior change and addiction treatment intervention, and he is particularly interested in the relationship between alcohol and HIV. Jasjit S. Ahluwalia, MD, MPH, MS, Deputy Director, and Core Leader, is a physician and population health/public health scientist. He has been a practicing physician, faculty member, department chair, and Associate Dean. He has served as PI of an NIH Center of Excellence on Minority Health and Health Disparities and as Associate Director of the University of Minnesota's CTSA grant, directing education, training, and career development. He most recently served as a School of Public Health Dean. His primary research has focused on nicotine addiction and smoking cessation in African-American smokers.

The Administrative Core provides an organizational structure for the CADRE, state-of-the-art mentoring for CADRE Project Leaders (PLs) and Pilot PLs, a Pilot Project Program, supports diversity and health disparities work, and leads CADRE's evaluation effort. The Core creates an environment that promotes and encourages scientific exchange and innovation in the realm of substance use and chronic disease. Core personnel work with PLs to prepare competitive grant proposals and peer-reviewed manuscripts emanating from CADRE-sponsored research. The Core brings nationally-known distinguished scholars to the Brown campus each year to present to the extended academic community.

By its nature, COBRE's operate such that once a PL obtains an independent research grant, e.g., an R01, she/he "rotates off" salary funding from the COBRE grant. Thus, an important task of the Executive Committee is to solicit and organize the selection of replacement PLs. This is done in consultation with a distinguished External Advisory Committee.

CLINICAL LABORATORY CORE

Jennifer W. Tidey, PhD, lead, the Clinical Laboratory Core, Associate Dean for Research at the Brown School of Public Health, Associate Director of CAAS's Drug Abuse T32 Training Program, and Director of the CAAS Laboratory. Dr. Tidey is a translational addictions scientist who focuses on developing and testing interactive models of biological, social, and environmental variables to understand the etiology and persistence of SUDs. Her work has assessed the behavioral, subjective, and physiological effects of opioids, psychomotor stimulants, alcohol, and nicotine/tobacco,

in studies based on conditioning and behavioral economic theories of addiction. Her work spans multiple intervention development stages – from basic science, to intervention generation, and pilot testing, to traditional efficacy testing, to policy-informed research.

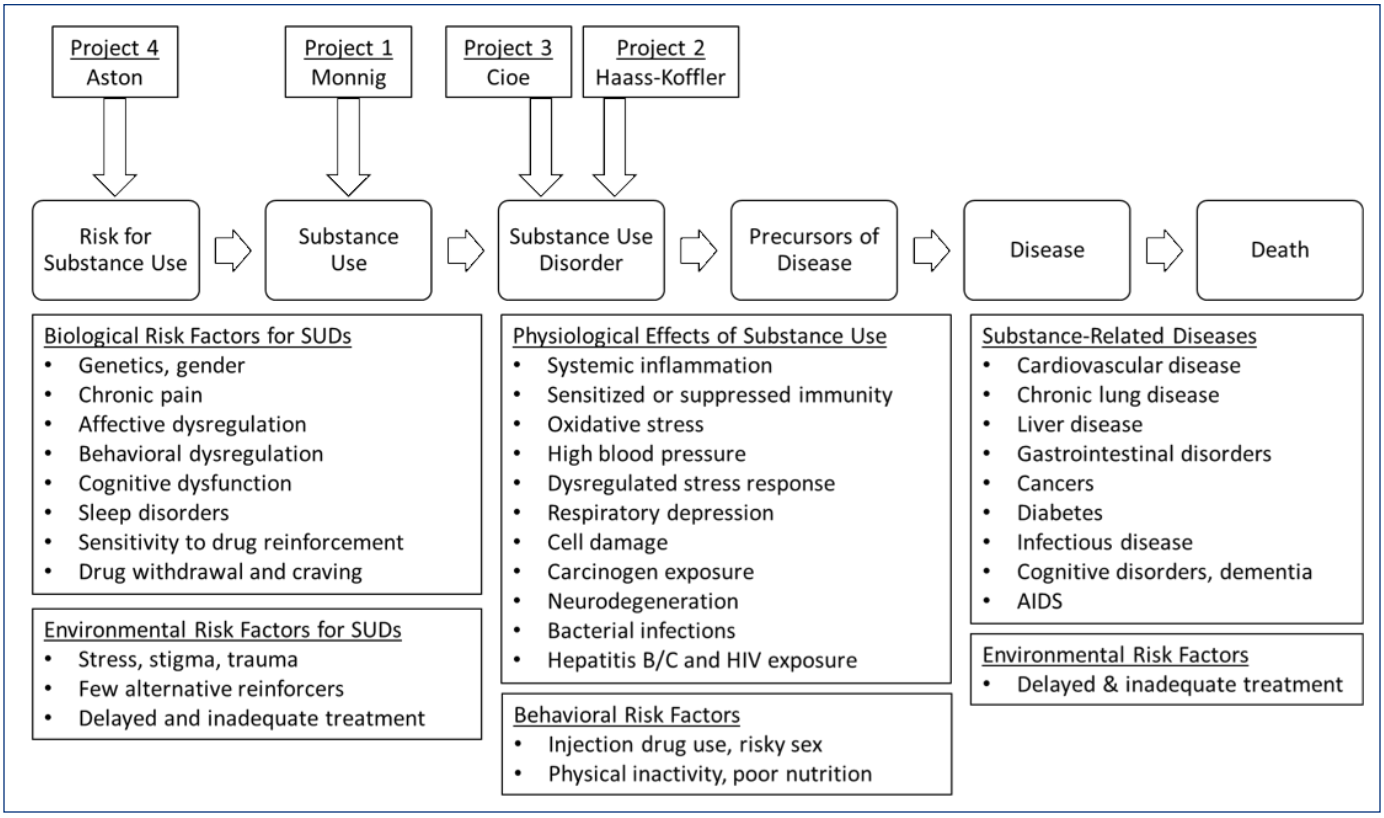
The Clinical Laboratory Core facilitates the goals of the major projects and pilot projects and benefits the broader Brown community, by providing infrastructure, resources, and scientific expertise, in the service of developing and sustaining a multi-disciplinary center. It maximizes CADRE's efficiency and cost-effectiveness by creating linkages between CADRE's Research Projects and other COBREs. Additionally, it is creating a center-wide data base of risk factors associated with development and progression of SUDs and chronic disease available to CADRE PLs and others engaged in research consistent with CADRE's mission. This center-wide database consists of biopsychosocial assessments collected across projects to allow for the formulation and testing of multi-causal models of relationships between SUDs and chronic disease. Further, through NIGMS funding, supplemented by institutional funds, we have made significant renovations to the CAAS Laboratory and purchased major state-of-the-science equipment to meet the ever-growing needs and technical capability of the CADRE.

CADRE RESEARCH PROJECTS

CADRE originally consisted of four thematically and technically linked research projects (RPs) led by an interdisciplinary group of early-career faculty. These RPs and their relationship to biological risk factors, physiological effects, and substance-related diseases are depicted in **Figure 1.**

Mollie Monnig, PhD, Research PL, is a clinical psychologist and Assistant Professor of BSS at CAAS. Dr. Monnig's primary research objective is to advance understanding of alcohol's effects on the gut-brain axis in the context of HIV. In her CADRE project, Dr. Monnig is examining acute neural and immune effects of alcohol in PLWH. Given the dearth of experimental research on alcohol use in PLWH, it is not known whether alcohol exacerbates immune dysfunction in this population. Monnig examines whether alcohol stimulates acute inflammatory responses along the gut-brain axis and compares alcohol's effects on immune biomarkers and neurobiological outcomes in PLWH and healthy controls. This multidisciplinary framework will enable the detection of temporally related changes through measurement of plasma biomarkers of microbial translocation and immune activation and MRI measures of neurometabolic, white matter diffusivity, and extracellular water, consistent with alcohol-induced inflammation in the peripheral immune system and brain.

Figure 1. CADRE conceptual model indicating biopsychosocial mechanisms underlying the linkages between substance use and chronic disease, and where the aims of the initial CADRE research and pilot projects fit on this continuum.



Elizabeth Aston, PhD, Research PL, received a PhD in Neuroscience from Wake Forest School of Medicine and is currently an Assistant Professor of BSS at CAAS. Dr. Aston's primary research objective is to examine predictors of cannabis use disorder severity among regular marijuana users and the relative reinforcing value of marijuana using a behavioral economic marijuana purchase task. In her CADRE project, Dr. Aston examines the effects of cannabis on rheumatoid arthritis pain, affect, and inflammation and investigates whether the effects of cannabis on pain and affect are mediated via the effects of cannabis on inflammatory biomarkers. As such, her study is motivated by a looming concern that some analgesic pharmacotherapy classes have limited efficacy in pain treatment and, in the case of opioids, have significant abuse liability.

Patricia Cioe, PhD, an Assistant Professor of BSS at CAAS with a background in nursing research, was part of the original CADRE application and had proposed in her CADRE project to examine the effects of electronic nicotine delivery systems (ENDS) in PLWH, who are not motivated to quit smoking. PLWH have increased cardiovascular disease rates, pulmonary disease, infection and lung cancer relative to the general population. Outcomes were to include smoking as well as effects on biomarkers of cardiac disease, pulmonary disease, and carcinogen exposure. Dr. Cioe rotated off the CADRE once her U01 was funded to conduct a similar (though more extensive) study to that proposed for the CADRE.

Carolina Haass-Koffler, PharmD, is an Assistant Professor of Psychiatry and Human Behavior and BSS at CAAS and came to CADRE with a strong background in pharmacology and neuroscience. Dr. Haass-Koffler is a translational investigator who integrates preclinical and clinical research to examine the biobehavioral mechanisms of addiction toward developing novel medications. For her CADRE project, Dr. Haass-Koffler proposed translating a validated preclinical paradigm (yohimbine-induced stress) to human laboratory research and pairing it with a human laboratory paradigm (cue reactivity) to investigate whether the anti-stress hormone, oxytocin, reduces opioid craving during stress induction. Dr. Haass-Koffler rotated off the CADRE as a PL once an R01 was recently awarded to her by NIAAA. However, as described below, CADRE has funded a pilot study of reduced scope to the initially proposed research.

Hayley Treloar Padovano, PhD, pending PL, is a clinical psychologist and Assistant Professor of Psychiatry and Human Behavior and BSS at CAAS. Dr. Treloar Padovano's research program's long-term goal is to develop more effective interventions to promote alcohol abstinence and prevent relapse in AALD patients. For her CADRE project, Dr. Treloar has recently proposed to examine alcohol-associated liver disease (AALD) and drinking in patients suffering from AALD. She proposes a prospective, two-arm intervention study comparing patients with AALD/AUD vs. those with AUD only. Ecological momentary assessment and a human laboratory paradigm will assess biomarkers of inflammation and immune response and behavioral AUD endophenotypes in the setting of a brief motivational intervention targeting drinking. This project has received approval from CADRE's External Advisory Board and is in the final stages of NIGMS approval.

CADRE PILOT PROJECTS

Carolina Haass-Koffler, PharmD, is examining the initial efficacy of oxytocin as a potential pharmacotherapy for opioid use disorder, as described above.

Mollie Monnig, PhD, is examining participants' experiences and substance use behavior during the Coronavirus pandemic in the context of a community/longitudinal survey. As Dr. Monnig is a CADRE PL, her pilot study is funded with institutional funds rather than by NIGMS.

A third pending pilot project has been approved internally and is awaiting final approval from NIGMS.

SUMMARY

As shown in the above-listed projects, our CADRE has been very productive during its initial 18 months. Indeed, we have published 22 manuscripts to date. We are fortunate to have excellent, interdisciplinary PLs and an impressive pipeline for future potential early career applicants. Two of our original PLs have "graduated," and the remaining PLs have R01s in various stages of submission. We have two replacement PL's pending NIGMS approval. Through our Laboratory Core, the provision of resources and expertise is a highly sought-after feature of CADRE, one which already is in high demand by non-CADRE faculty. Given the innovative theme of the CADRE, biopsychosocial mechanisms linking SUDs and chronic illness, and the prevalence of substance use and chronic disease, scientific contributions emanating from CADRE should be of high public health significance and therefore should accelerate the careers of our faculty. We anxiously await our initial studies' results and look forward to sharing them with the scientific community.

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Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect the views of the National Institute of General Medical Sciences.

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The Center of Biomedical Research Excellence (COBRE) for Perinatal Biology – Accomplishments, Impact, and Long-term Results

SUNIL K. SHAW, PhD

ABSTRACT

The COBRE for Perinatal Biology (CPB) was the third grant in Rhode Island to be funded by the COBRE mechanism. The CPB was based at Women & Infants Hospital, and housed in the Kilguss Research Institute, in the Jewelry District in Providence. The scientific focus of the CPB was on perinatal diseases such as preeclampsia and preterm birth, as well as more broadly on cardiopulmonary development and reproductive biology. Over the course of three phases and 17 years, the CPB funded 22 projects. CPB investigators, in turn, generated over $27.5 million in independent funding from federal and non-federal sources. Besides providing scientific and career mentorship to new investigators in Rhode Island, the CPB established a Research Core. The Kilguss Research Core remains active and flourishing and provides advanced imaging, molecular biology and flow cytometry abilities to researchers at Women & Infants as well as the greater Rhode Island scientific community.

KEYWORDS: cardiopulmonary development, reproductive biology, perinatal biology, mentoring

INTRODUCTION

Congress established the Institutional Development Award (IDeA) program to promote research in states that historically had low success rates in National Institutes of Health (NIH) funding. The Centers of Biomedical Research Excellence (COBRE) funding mechanism was designed by the NIH in response to support the development of cutting-edge research centers in IDeA states.[1] Women & Infants Hospital is the primary provider of tertiary perinatal services in Southeastern New England. The Hospital maintains accredited residency and subspecialty training programs in obstetrics and gynecology, pediatrics, and developmental pathology. Hospital leadership recognized that preeminent basic research programs always accompany clinical excellence at leading hospitals in the US. Matching the Hospital's clinical expertise with the funding opportunity led to the award for the COBRE for Perinatal Biology (CPB) in 2003. The COBRE's scientific focus was on basic research on pregnancy and development, and translational research on therapeutic strategies to treat their associated diseases. The CPB was the anchoring award for the newly opened Kilguss Research Institute at Women & Infants. Over the next 17 years, the COBRE founded a Center for Perinatal Biology, mentored new investigators, and established a Research Core.

PHASE I (2003–2008)

Directed by James Padbury, and with Surendra Sharma as Deputy Director, the first phase of the CPB supported four major projects and five smaller pilot projects (**Table 1**). During this period, COBRE investigators published 47 publications in peer-reviewed journals, and seven went on to achieve independent funding. Additionally, the CPB established a Research Core focusing on developing molecular biology, histology, and imaging instrumentation and techniques for the Kilguss Institute. The author of this article was recruited as Associate Director for the Research Core during Phase I and provided a technical focus on microscopy and live-cell imaging.

Research Project I was led by Lazaros Kochilas, "Role of p57KIP2 in Cardiomyocyte Differentiation". This project focused on this cyclin-dependent kinase inhibitor, also known as CDKN1C, and the differentiation of ventricular myocytes. The project proposed to study p57KIP2 physiologic expression and over-expression in murine and zebrafish models of heart development. The project's significance lies in the potential role for this protein in dilated cardiomyopathy, ventricular hypertrophy and translationally in cardiac regeneration. Dr. Kochilas is now a full professor at Emory University in Atlanta, and is the Medical Director of Cardiac Clinical Research.

Yi-Tang Don Tseng led Project II, "Signaling Pathways Regulating Cardiomyocyte Proliferation". This project focused on the β1-adrenergic receptor, phosphoinositide 3- kinase and extracellular signal-related kinases and cardiac growth regulation during gestation and postnatal development in a mouse model. Translational aspects lay in the potential for reinitiating cardiomyocyte differential proliferation in adults after damage.

Project III was led by Juan Esteban, "Mechanotransduction and lung alveolar differentiation". This project focused on intra-uterine fetal breathing movement, mechanosensing via EGFR and subsequent differentiation of type II lung epithelial cells in a murine model. Translational aspects lay in potential therapies for pulmonary complications in premature infants with underdeveloped lungs.

Table 1. COBRE for Perinatal Biology Investigators and Projects

Phase I			
Project I	Lazaros Kochilas, MD	2003-2008	Role of p57KIP2 in Ventricular Cardiomyocyte Differentiation
Project II	Yi-Tang Tseng, PhD	2003-2008	Signaling Pathways Regulating Cardiomyocyte Proliferation
Project III	Juan Sanchez-Esteban, MD	2003-2008	Mechanotransduction and Lung Alveolar Differentiation
Project IV	Monique DePaepe, MD	2003-2008	Role of Fas -Mediated Apoptosis in Perinatal Lung Remodeling
Pilot I	Ting C. Zhao, MD, PhD	2004-2008	Transcriptional Regulation of the β1AR by c-Myc
Pilot II	Zhongbin Lai, MD, PhD	2006-2008	Genetic Mouse Models of Preeclampsia
Pilot III	Edward Chien, MD	2006-2008	Biomechanical Molecular Events in Cervical Remodeling
Pilot IV	Mary Hixson, PhD	2006-2008	Examination of Neonatal Stress Response Genes following intrauterine MEHP-Induced Testicular Injury
Pilot V	Jonathan Kurtis, MD, PhD	2006-2008	Mechanism of Schistosome-Associated Trophoblast Injury

Phase II			
Project I	Joseph Bliss, MD, PhD	2008-2013	Neonatal Candidiasis and Immune Compromise during Development
Project II	Jared Robins, MD	2008-2013	Programming Trophoblast Differentiation and Invasion by Multiple Oxygen Pathways
Project III	Ting Zhao	2008-2009	The role of PI3 kinase in myocardial remodeling and regeneration
Project IV	Carmen Marsit, PhD	2008-2012	Epigenetic Alterations as Markers of the Intrauterine Environment
Pilot I	Satyan Kalkunte, PhD	2008-2012	Novel Animal Models of Preeclampsia
Pilot I	Shibin Cheng, MD	2012-2013	Novel Animal Models of Preeclampsia
Pilot II	Sunil Shaw, PhD	2009-2013	Uterine NK Cell Homing from the Peripheral Circulation
Pilot III	Beatrice Lechner, MD	2011-2013	The Role of Biglycan and Decorin in Preterm Birth
Pilot IV	Peng Zhang, PhD	2011-2013	Reactivation of Fetal/Early Postnatal MicroRNA Program in Adult Cardiac Fibroblasts during Cardiac Remodeling
Pilot V	Eric Morrow, MD, PhD	2011-2013	Trafficking Mechanisms and Axonal Growth in Embryonic and Perinatal Development

Phase III			
Pilot I	Yi-Tang Tseng, PhD	2015-2019	A novel PRKAG2 mutation- an early-onset hypertrophic cardiomyopathy phenotype and treatment
Pilot II	Joseph Bliss, MD, PhD	2015-2020	Contribution of Galectin-3 to Host Defense against Neonatal Candidiasis
Pilot III	Tanbir Najrana, PhD	2015-2020	Role of mechanical stretch induced EV-miRNA in lung development
Pilot IV	Martin Keszler, MD	2015-2020	NIPPV vs. CPAP at equal mean airway pressure
Pilot V	Jin O-Uchi, PhD	2016-2017	Role of mitochondrial calcium and ROS in the early postnatal cardiac development

Dr. Esteban is now Associate Professor of Pediatrics at Brown University/Women & Infants.

Project IV was led by Monique DePaepe, "Role of Fas-mediated Apoptosis in Perinatal Lung Remodeling". This project focused on testing if apoptosis of alveolar type II cells was necessary for lung development and differentiation in a murine model. Translational aspects lay in potential therapies for bronchopulmonary dysplasia in newborns. Dr. DePaepe is now Professor of Pathology and Laboratory Medicine at Brown University/Women & Infants.

Pilot I was led by Ting Zhao, "Transcriptional Regulation of the β1AR by c-Myc". This project focused on myocardial ischemic injury and β1AR and PI3K signaling roles in recovery. Dr. Zhao is now Associate Professor of Surgery at Boston University.

Pilot II was led by Zhongbin Lai, "Genetic Mouse Models of Preeclampsia". In this project, IL-10 knockout mice treated with preeclampsia serum were established as an animal model of preeclampsia. The generation of an animal model for this human disease has already led to a better understanding of this disease and more effective therapies for treatment and diagnosis.

Pilot III was led by Edward Chien, "Biomechanical molecular events in cervical remodeling". This project focused on cervical ripening and its role in preterm birth, and glycosaminoglycan changes associated with it in a rat model. Dr. Chien is at Cleveland Clinic in Ohio, at the Women's Health Institute.

Pilot IV was led by Mary Hixson, "Examination of Neonatal Stress Response Genes following intrauterine MEHP-Induced Testicular Injury". This project focused on the effect of phthalates on male germline cells during development. Dr. Hixson is a Senior Toxicologist at Gradient Corporation in Boston.

Pilot V was led by Jonathan Kurtis, "Mechanism of Schistosome-associated trophoblast injury". This project focused on the effect of Schistosoma antigens on primary human trophoblasts in vitro. Dr. Kurtis is now Professor and Chair of the Department of Pathology and Laboratory Medicine at Brown University and Director of the Lifespan Center for International Health Research.

PHASE II (2008–2013)

During Phase II, a new round of four major and five pilot projects was initiated. During this period, COBRE investigators published 156 articles in peer-reviewed journals, and 9 went on to achieve independent funding. The Research Core expanded its user base and added expertise in microscopy to include live-cell imaging.

Project I was led by Joseph Bliss, "Neonatal Candidiasis and Immune Compromise during Development". The focus of this project was on developing a model for *Candida albicans* infections in neonatal mice. Translational aspects lay in understanding mechanisms of disease in and identifying potential therapies for the most common fungal infection in premature and term neonates. Dr. Bliss is now Professor of Pediatrics and Director of the Fellowship Program in Neonatal and Perinatal Medicine at Brown University.

Jared Robins led Project II, "Programming Trophoblast Differentiation and Invasion by Multiple Oxygen Pathways". This project focused on the role of hypoxia during remodeling of placental and uterine vasculature by trophoblasts. Dr. Robins is now Associate Professor of Obstetrics and Gynecology and Chief of the Division of Reproductive Endocrinology and Infertility at Northwestern University.

Project III was led by Ting Zhao, "The role of PI3 kinase in myocardial remodeling and regeneration". This project

focused on myocyte proliferation and hyperplasia and the effect of PI3 kinase. Dr. Zhao is now a Professor of Surgery at Boston University.

Project IV was led by Carmen Marsit, "Epigenetic Alterations as Markers of the Intrauterine Environment". This project focused on DNA methylation analysis of placental tissue as a marker of environmental toxicants. Dr. Marsit is now Professor of Environmental Health at the Rollins School of Public Health, Emory University.

Pilot I was initially led by Satyan Kalkunte, "Novel Animal Models of Preeclampsia". This project identified that misfolding of the serum protein transthyretin contributed to preeclampsia. After Dr. Kalkunte entered a job in industry, the project was led by Dr. Shibin Cheng. Dr. Cheng is now Associate Professor of Pediatrics at Brown University/Women & Infants.

Pilot II was led by the author, "Uterine NK Cell Homing from the Peripheral Circulation". This project focused on adhesion molecules expressed by Natural Killer cells, and their migration from the peripheral circulation into the uterus during early pregnancy.

Pilot III was led by Beatrice Lechner, "The roles of Biglycan and Decorin in Preterm Birth". This project's focus was the small chondroitin sulfate/dermatan sulfate proteoglycans that are necessary for structural integrity of the fetal membranes, and testing if their loss led to premature membrane rupture and preterm birth. Dr. Lechner is an Associate Professor of Pediatrics at Brown University/Women & Infants.

Peng Zheng led Pilot IV, "Reactivation of Fetal/Early Postnatal MicroRNA Program in Adult Cardiac Fibroblasts during Cardiac Remodeling". The focus of this project was to examine the role of microRNAs in fetal and adult heart function. Dr. Zhang is an Assistant Professor of Medicine at Lifespan/Brown University.

Pilot V was led by Eric Morrow, "Trafficking Mechanisms and Axonal Growth in Embryonic and Perinatal Development". This project focused on endosomal Na+/H+ exchanger 6 (NHE6), and its role in reduced branching in axonal and dendritic branching in an autism-type disorder. Dr. Morrow is now the Mencoff Family Associate Professor of Biology, Associate Professor of Neuroscience, Associate Professor of Psychiatry and Human Behavior at Brown University.

PHASE III (2015–2020)

Phase III of the CPB was initially led by James Padbury, who stepped down to lead the Advance-CTR Award. The project was then led by Surendra Sharma, who later stepped down to lead the COBRE for Reproductive Health. For its last three years, CPB has been led by Sunil Shaw, the author. During this phase, only pilot projects were permitted, and five were funded, resulting in 15 peer-reviewed publications. During this period, the Research Core transitioned to a fee-for-use shared equipment model and significantly widened its user base. Phase III ended in 2020, and is currently in no-cost extension.

Pilot I was led by Don Tseng, "A novel PRKAG2 mutation – an early-onset hypertrophic cardiomyopathy phenotype and treatment". This project focused on a functional mutation within the γ2-subunit isoform of 5′-AMP-activated protein kinase (AMPK), which resulted in hypertrophy that was reversed with rapamycin.

Pilot II was led by Joseph Bliss, "Contribution of Galectin-3 to Host Defense against Neonatal Candidiasis". The project's focus was on the S-type lectin receptor, Galectin-3, and its role in defense against the fungal pathogens *C. albicans* and *parapsilosis*.

Tanbir Najrana led Pilot III, "Role of mechanical stretch induced EV-miRNA in lung development". This project focused on microRNAs expressed in lung extracellular vesicles, and their role in differentiation of epithelial cells. Dr. Najrana is an Investigator in Pathology and Laboratory Medicine at Lifespan/Brown University.

Pilot IV was led by Martin Keszler, "NIPPV vs. CPAP at equal mean airway pressure". This project compared two ventilation methods, continuous positive airway pressure (CPAP) and noninvasive positive pressure ventilation (NIPPV). Dr. Keszler is a Professor of Pediatrics at Brown University/Women & Infants.

Pilot V was led by Jin O-Uchi, "Role of mitochondrial calcium and ROS in early postnatal cardiac development". This project focused on calcium signaling and reactive oxygen species in cardiomyocytes. Dr. O-Uchi is Assistant Professor of Medicine in Cardiology at the University of Minnesota.

KILGUSS RESEARCH CORE

The Research Core for the CPB remains active and provides advanced imaging and molecular biology capabilities to researchers at Women & Infants Hospital, Brown University, and affiliated institutions. Academic researchers are billed at uniform rates for equipment maintenance and supplies. The Core also serves researchers from for-profit laboratories. Core staff provides training and consultation in experimental design, data interpretation and analysis, and presentation. The Kilguss Research Core offers several unique capabilities that are not widely available in Rhode Island. A detailed listing of core equipment is available at coresri.org, and equipment may be scheduled on a web-based service, facilitating billing and use by researchers outside the Kilguss Institute.

CONCLUSION

Over 3 phases spanning 17 years, the COBRE for Perinatal Biology has supported a cadre of researchers and projects in the fields of reproductive biology, development, and perinatal diseases such as preeclampsia and preterm birth. It has left a lasting positive impact on junior investigators' careers and helped develop basic and translational research in Perinatal Biology at Women & Infants Hospital and throughout the state of Rhode Island. COBRE and INBRE grants have provided an important boost to research and continue to play a critical role in building a scientific workforce that will continue to enhance the local economy on a sustainable and long-term basis.

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Rhode Island COBRE Center for Central Nervous System Function: Progress and Perspectives

JEROME N. SANES, PhD

ABSTRACT

The Center of Biomedical Research Excellence (COBRE) Center for Central Nervous System Function (CCNSF) was funded in 2013 by the National Institute for General Medical Sciences to establish a collaborative environment for basic and applied research in higher nervous system function with humans and experimental animal model systems. Since its inception, the COBRE CCNSF has funded junior faculty investigators as Project and Pilot Project Leaders and one established investigator on projects investigating fundamental properties of nervous system function using a range of tools spanning molecular genetics, neurophysiology, invasive and non-invasive brain stimulation, behavior and neuroimaging. The Administrative Core facilitates all Center activities with a focus on career development, grant proposal submission, and deployment of technology developed by our research cores. The Design and Analysis Core aims to provide principled study design expertise, statistical modeling, machine learning, inference, and computation. The Behavior and Neuroimaging Core provides project-specific collaboration and support to COBRE scientists to promote the acquisition of high quality behavioral, physiological, neuroimaging and neurostimulation data, to ensure the integrity of the data collection infrastructure and to help implement robust data processing and visualization pipelines. While the cores principally serve Center scientists, our Center and the core resources have availability to all Rhode Island researchers.

KEYWORDS: neural function, neural recording, neuroimaging, behavior, core services

INTRODUCTION

Higher brain function often refers to the general ability to plan, organize, and select behaviors in a goal-directed manner.[1-5] Deficits in higher brain function are common in both neurological and psychiatric disorders. They can result in a wide range of higher-order behavioral deficits, including an inability to plan a purposeful sequence of actions, a failure to inhibit inappropriate or detrimental responses, and difficulty initiating or flexibly shifting to novel responses as task demands change.[2,6-8] These high-level deficits can occur following a stroke, brain damage, or neurological diseases, including Alzheimer's disease[9] and Parkinson's disease.[10] Moreover, many psychiatric disorders result in high-level cognitive deficits, such as schizophrenia[11] and attention-deficit hyperactivity disorder.[12]

The American Psychiatric Association's definition of dementia (DSM IV) includes executive dysfunction (synonymous with deficiencies in high-level brain function).[13] However, specific diagnosis and clinical assessment remain difficult. The limited understanding of the neural systems' specific organizations mediating high-level function and its underlying mechanisms may contribute to this problem. For example, the Research Council of the American Neuropsychiatric Association conducted a comprehensive, clinically-oriented review of research from 1966 to 2002 on higher brain function. It concluded that a lack of basic knowledge into its mechanisms, functional organization and diversity remained a persistent obstacle to clinical assessment and treatment.[14] Since that time, the basic mechanisms of attention, decision, and action have received growing interest, and these have formed the core of our COBRE project.

Integration of psychophysics, genetic tools, and neuroimaging represents a fundamental approach to address clinically significant gaps in the basic understanding of high-brain function. A significant obstacle to understanding higher brain function arises from uncertainty about how defining its major components, some of which – attention, decisions and action – we focused upon in Phase 1 of our COBRE project. Functional neuroimaging methods can measure the impact of a particular cognitive manipulation on activation in a specific brain region. Therefore, differences in developmental and adult-level attention, decision and action functions may be indexed by changes in activation in different brain regions or networks. Second, functional neuroimaging, neural recording, and intracranial stimulation can reveal how brain areas interact during the elaboration of these key processes. Attention and decision-making often operate through top-down modulation of ongoing processing, such as in the primary visual cortex or lateral temporal cortex. The impact of these top-down modulatory effects on local processing is difficult to assess using behavioral measures alone. However, functional MRI, source localized EEG, and combined neural recording and intracortical stimulation,

coupled with contemporary analysis methods, can permit measurement of local changes in targeted regions, such as the primary visual cortex, due to top-down modulation. This offers a means of studying the mechanisms and dynamics of top- down control. Finally, the ability to precisely localize higher brain function to neocortical and subcortical sites using functional neuroimaging permits more specific predictions regarding the impact of neurological and psychiatric disorders on higher brain function and the potential effects of behavioral and pharmacological interventions on these deficits. Integrating genetic analysis provides the opportunity to probe how genetic variations shift the parameters of these various components of higher brain function, which is essential for understanding variability across natural human populations.

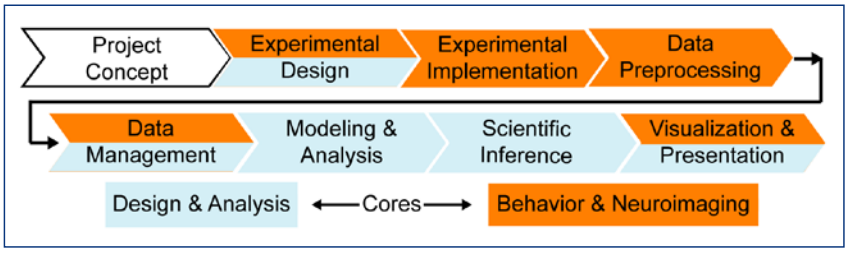
ORGANIZATION OF THE COBRE CCNS

When we considered applying to the National Institute for General Medical Sciences (NIGMS) for COBRE funding, Brown University had significant research activities concerned with higher central nervous system function. Nevertheless, we believed that Brown and its affiliated hospitals and the larger Rhode Island community, could benefit by establishing a research center focused on nervous system function especially that related to cognition in health and brain disorders. We, therefore, proposed establishing a Center for Central Nervous System Function (CCNSF) to develop infrastructure in two domains: faculty researchers, particularly junior investigators, who would serve as Project Leaders (PL) and Pilot Project Leaders (PPL), and research cores, designed to facilitate the development of the research programs of PLs and PPLs.

Like all COBRE Centers, we established the obligatory Administrative Core. This core, with input from our Internal Advisory and External Advisory Committees, aims to support the scientific, technical and mentoring goals of our COBRE Center by providing leadership and an administrative structure to facilitate and coordinate the activities of the leaders of each research project, the overall Principal Investigator, the Deputy, and Associate Directors, positions held respectively by David Sheinberg (professor, Department of Neuroscience) and John Davenport (Managing Director, Carney Institute for Brain Science). The Administrative Core, among other functions, provides administrative support for the Principal Investigator and all PLs, PPLs, and Core Directors, collection and maintenance of financial records for all projects and cores; prepares the annual Progress Report; coordinate activities of the Internal Advisory Committee, the University Advisory Committee, and the External Advisory Committee in their roles of mentoring and evaluating the research and personnel in each project and core; organizes the COBRE Center's internal meetings, and assists in data dissemination and sharing. Additional activities may include interactions with relevant departments and programs in faculty searches, external seminar series, and internal journal clubs. Indeed, we have used COBRE funds for the recruitment of one PL (T. Desrochers) and have made commitments to two incoming tenure-track faculty, pending NIGMS approval.

For the initial four years of Phase 1, we had a single research core, the Design and Analysis Core (DAC), and this core has continued into Phase 2. Applied scientists from Brown's Department of Biostatistics, Division of Applied Mathematics, and the Department of Computer Science have directed the DAC. The primary purpose of the DAC concerned developing novel analytic tools for designing experiments and analyzing data, all in the service of the specific experiments proposed and implemented by PLs and PPLs. This core had more of a research-slanted focus compared to the typical service-related emphasis of COBRE research cores, aiming to develop collaborations with PLs and PPLs. We expected that the DAC would also provide more prosaic statistical and data science queries related to experimental design and data analysis implements. The core has succeeded in generating many original publications, more than 10 during Phase 1, and DAC staff have provided valuable consulting services to our PLs and PPLs. As Phase 1 progressed, and particularly due to input from PLs and PPLs, we recognized a need to enhance services related to implementation of research, especially for developing best practices to conduct experiments using structural MRI, task-based and resting state functional MRI, diffusion imaging, transcranial magnetic stimulation, transcranial direct-current and transcranial alternating-current stimulation, galvanic skin response, electroencephalography, and eye tracking. Clearly, the complexity of these techniques and the challenges of mastering the infrastructure required for effective and efficient deployment of them can significantly impede research progress, especially in the case of relatively junior investigators. Therefore, we created the Behavior and Neuroimaging Core (BNC) to provide ongoing expert support, training, assistance, and advice to

Figure 1. Project flow. PL or PPL brings a concept to DAC (light blue shading) and BNC (orange shading), which initiates a series of sequential steps from experimental design to final realization. Boxes with both orange and blue coloring indicate a cooperation between the two research cores.



the COBRE PIs and PPLs in the practical aspects of data collection, data management, and data processing.

Together, the DAC and BNC have provided support and assistance to COBRE PLs and PPLs and their research teams to promote and facilitate the acquisition of high-quality research data and facilitate analysis of COBRE research data through deployment of tools, analysis platforms, and training. **Figure 1** illustrates the typical flow for research projects from project inception through its completion. One notes that the DAC and BNC have overlapping and non-overlapping functions.

RESEARCH ACTIVITIES OF THE COBRE CCNSF

Since the inception of our COBRE in 2013, we have supported 11 PLs, eight in Phase 1, with two of these PLs spanning Phase 1 and Phase 2 and three solely in Phase 2. We will soon recruit at least two new PLs to "replace" PLs who will rotate off COBRE support. In the final years of Phase 2, we may recruit up to three other PLs for the total of 13 to 16 PLs who have or will have benefitted from COBRE support. **Table 1** lists Phase 1 and Phase 2 supported PLs, along with their primary academic department, their project title and their support term. The PLs have come from Brown University's Division of Biology and Medicine (MCB, Neuroscience, Neurosurgery), Arts and Sciences (CLPS), and School of Public Health (Biostatistics). All but W. Asaad and M. Worden had tenure-track appointments, with Neurosurgery (W. Asaad) not having tenure-track options and M. Worden serving in the research track. Most of the PLs conducted research with humans, spanning systems and cognitive neuroscience questions and addressing a wide range of questions from basic visual processing (M. Worden) to brain mechanisms of social interactions (O. FeldmanHall). Two PLs (W. Asaad and T. Desrochers) used non-human primates to investigate fundamental questions about learning, decision-making and mental sequences. Two PLs used other model systems (rodents and Drosophila) to investigate fundamental mechanisms underlying developmental disorders (E. Morrow) and the molecular genetics and neural circuit dynamics mediating reward behavior (K. Kaun).

Along with the eight awarded pilot projects (not listed), whose leaders had primary appointments in several different departments and Brown University divisions, including Neuroscience, CLPS, Psychiatry, and Behavioral and Social Sciences, the unifying theme of all projects and pilot projects concerned revealing brain mechanisms of higher central nervous system function in health and disease. The project led by K. Kaun exemplifies our approach. She uses fruit flies as a model system and employs standard and novel methods spanning behavioral analysis, neural circuit recording, and molecular genetics to learn basic reward mechanisms. For her COBRE project, Prof. Kaun proposed investigating a glutamate-dopamine feedback circuit responsible for reward prediction and the localization of dopamine-2 like receptors (D2Rs) within this circuit in Drosophila. She hypothesized that feedback from glutamate neurons would result in a sparse representation of reward dopamine neurons in-memory expression and that D2R localization in these dopamine neurons would change during memory consolidation. One aim focused on testing whether a mushroom body (a major component of the fruit fly's brain) γ5β'2 glutamate to dopamine connection is required for memory expression. A second aim proposed to develop a new tool for in vivo localization of D2Rs within this circuit. Other projects funded by our COBRE had similar focused and important goals.

Not listed in Table 1 are the genders of the Project Leaders: seven women and four men; the Pilot Project Leaders were roughly equally split between men and women. Following NIGMS's emphasis on building capacity, especially for junior investigators, all but Prof. Jones had junior investigator

Table 1. Project Leaders of the COBRE CCNSF

	Department*	Project Title	Tenure
Morrow, E.	MCB	Genetic-imaging study of obsessive compulsive behavior in autism	2013–2015
Amso, D.	CLPS	Development of vision and attention in typical and ASD individuals	2013–2016
Worden, M.	Neuroscience	Conflict adaptation and selective attention	2013–2017
Asaad, W.	Neurosurgery	Cortical-subcortical interactions in attention and learning	2013–2018
Song, J-H.	CLPS	Target selection for visually guided actions	2013–2018
Kaun, K.	Neuroscience	Microcircuits for reward driven decisions in Drosophila	2015–2018
Desrochers, T.	Neuroscience	The neural basis of sequence monitoring in human and nonhuman primates	2017–2021
Shenhav, A.	CLPS	Mechanisms of cognitive interference from value-based choice conflict	2017–2021
FeldmanHall, O.	CLPS	The neural and affective mechanisms of socially risky learning	2018–2021
Eloyan, A.	Biostatistics	Quantitative methods for brain connectivity network estimation and interference in functional magnetic resonance imaging	2018–2021
Jones, S.	Neuroscience	The causal role of neocortical beta events in human sensory perception	2018–2021

* MCB: Molecular Biology, Cell Biology and Biochemistry; CLPS: Cognitive, Linguistic and Psychological Sciences

status when COBRE support began. Prof. Jones was included in Phase 2, since she proposed to extend her computational-driven work into empirically based data collection related to predictions of her computational models. Similarly, we considered all Pilot Project Leaders as junior investigators since none had received an R01 or equivalent grant when starting their pilot project, though one Pilot Project Leader had a K99/R00 grant, which NIGMS consider as a research project grant.

OUTCOMES OF COBRE CCNSF

Our PLs and PPLs and research core members have been particularly productive in garnering external research funds, publishing peer-reviewed papers, and advancing their careers at Brown (and unfortunately for us, also elsewhere via recruitment), while also receiving professional recognition. Collectively and to date, our cohort of faculty researchers have published nearly 90 peer-reviewed papers supported by COBRE funds, including many in well-respected journals such as *Annals of Neurology, Cell Reports, Current Biology, eLife, Genetics, Journal of Neuroscience. Nature*, *Nature Communications*, *Nature Human Behaviour, Nature Reviews Neuroscience, Neural Computation, NeuroImage Neuron, PLoS Computational Biology, PLoS Genetics, PNAS,* and *Psychological Review*, among others. As a group, the PLs and PPLs have successfully leveraged their COBRE support to garner more than $22 million in external research support, mostly from the NIH, but also from the NSF and other Federal agencies as well as from private foundations (e.g., Simons Foundation). As our Phase 2 PLs and PPLs progress in their research, we expect additional grant awards; indeed, one of our PLs has received promising news of both an NIH and an NSF award, thereby increasing, by about $3 million, the total grant awards of our COBRE cohort. Our COBRE supposed PLs have also received recognition for their outstanding work by being awarded tenure (Amso, Kaun, Morrow, Song) at Brown. In contrast, those supported in Phase 2 have made excellent progress toward tenure. For a loss to Brown but their benefit, some PLs and PPLs have been recruited to other institutions, even though Brown made competitive counteroffers. Some of our PLs have received national recognition, such as a PECASE award (E. Morrow) and field-specific young investigator citations (O. FeldmanHall and A. Shenhav). Taken together, our research cohort has made outstanding progress using the standard metrics of scientific achievement.

THE FUTURE OF THE COBRE CCNSF

As we reach the mid-point of the Phase 2 funding period, we have accelerated our Phase 3 application plans. To this end, we have identified a small cohort of PLs to "replace" graduating PLs for at least two years of project-level funding, using the faculty recruitment mechanisms provided by the COBRE program. Since Phase 3 COBRE grants provide only for pilot projects and cores, we have continued our outreach to inform department chairs and center and institute directors that we will have research funds for larger-scale pilot projects. We have also undertaken a review of our research cores' effectiveness, as we position them for the Phase 3 application. First, we have opened our cores to the entire Brown community, including Brown-affiliated hospitals and, with time, the whole Rhode Island scientific community, with an aim to demonstrate usage and need. Second, we have begun discussing how to leverage expertise in other COBRE Centers that use similar or related methodologies employed by our CCNSF researchers. Along these lines, we note that many NIGMS-funded IDeA programs have data handling capabilities, sometimes in the form of cores. We endorse efforts to coordinate data science expertise across the many COBRE and other IDeA supported programs (INBRE and CTR). The objective is to seek partners related to leveraging resources, especially financial ones and to demonstrate to the staff of NIGMS's Division for Research Capacity Building that the funds devoted to Rhode Island are being used well. Regarding the future of our research cores, in recognition that Phase 3 cores should focus on developing sustainability, we will refocus the DAC more toward service and less toward creating novel statistical approaches. Recall that, at the end of Phase 1, we split our DAC into two cores, one to develop theoretical approaches for experimental design and data analysis, the original main feature of the DAC, and the BNC to serve the practical needs of our COBRE cohort for experimental implementation. We now believe that we should reintegrate these two cores while maintaining efforts on developing novel statistical tools and integrating, but to integrate these efforts with those of other COBRE and other IDeA programs in Rhode Island.

We close with gratitude toward NIGMS for providing generous funds to foster the careers of many junior investigators in Rhode Island by providing direct support to their research endeavors and supporting research cores that have served our COBRE cohort.

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Advance-CTR: Statewide Infrastructure to Improve Health in Rhode Island through Clinical and Translational Research

VALERIE ZABALA, PhD; GABRIELLE STRANIERI, BA; HEATHER FOURNIER, MA; EDWARD HAWROT, PhD; JAMES PADBURY, MD

ABSTRACT

The universities, hospitals, government agencies, and community organizations in Rhode Island (RI) are well-positioned to bridge gaps between basic and clinical science. RI's manageable size, population demographics, and organizational structure present opportunities to test and implement impactful, transformative clinical and translational research. However, the state's resources had not been optimally coordinated to develop a multi-institutional, clinical and translational research infrastructure to improve clinical practice effectiveness and impact health care in RI. The objective of Advance Clinical and Translational Research (Advance-CTR) is to bridge these gaps by creating a statewide hub to coordinate and leverage existing research resources and provide new career development support and funding for academic researchers, particularly junior investigators. Research support offerings are responsive to a wide variety of needs and readily available via a service request form on AdvanceCTR.org, the first of its kind on a statewide level.

KEYWORDS: institutional development award, clinical and translational research, junior investigator funding, research services hub, NIGMS

INTRODUCTION

In 2016, Advance-CTR was created as a statewide network of academic and hospital partners, funded (U54GM115677) through the Institutional Development Award Program Infrastructure for Clinical and Translational Research (IDeA-CTR) established by the National Institute of General Medical Sciences (NIGMS). The IDeA-CTR program has three aims to ultimately address state health needs, particularly within medically underserved communities: (1) provide infrastructure and resources for clinical and translational research, (2) develop competitive clinical and translational research programs, and (3) promote clinical and translational research collaborations.1 Advance-CTR offers complimentary research resources and services to investigators and provides statewide awards programs aimed toward junior investigators that offer career development and mentoring. Requests for applications for awards and announcements for professional development opportunities and training are listed on AdvanceCTR.org and promoted in the Advance-CTR weekly newsletter. Using an online form, researchers can request guidance from experts to design and conduct clinical trials and observational research, use health care databases, apply advanced methods for statistical analysis, and engage research participants.

Following receipt of its award, Advance-CTR first sought to identify barriers to clinical and translational research in Rhode Island (RI) through a survey of investigators across our statewide partner network.2 Prominently, investigators identified the absence of pilot funding for broad clinical research, the lack of accessible biostatistics support, limited biomedical informatics expertise, and the challenge of sufficient protected research time as major obstacles (**Figure 1**). The survey found limited general awareness of the availability of the state's Core research services and instrumentation. Respondents also reported a lack of in-patient research facilities, general clinical research infrastructure, NIH-funded clinical research mentors, and programmatic support for clinical and translational research. In response to the needs assessment survey results, the Awards and Service Cores of Advance-CTR created resources, increased communication between its partner institutions, and enhanced pre-existing resources. Each partner site was provided a customized report highlighting results specific to their institution.

Most recently, RI's most vulnerable populations have been highly affected by the COVID-19 pandemic. Partnerships between the academic medical centers, the Department of Health, and the state government have led to early, robust participation in national medication, vaccine, and plasma-based clinical trials. Advance-CTR has sponsored supplemental applications to address the impact of COVID-19 on harm prevention organizations, the creation of a regional biobank that collaborates with the national IDeA-CTR consortium, participation in the National COVID Cohort Collaborative (N3C) data registry (ncats.nih.gov/n3c), and implementation of a National Institutes of Health (NIH) Rapid Acceleration of Diagnostics-Underserved Populations (RADx-UP) initiative aimed at addressing the disproportionate impact of COVID-19 on the Latinx community in RI (3U54AG063546-02S2). Advance-CTR will continue to support research responsiveness to emerging RI health concerns through its services and partnerships.

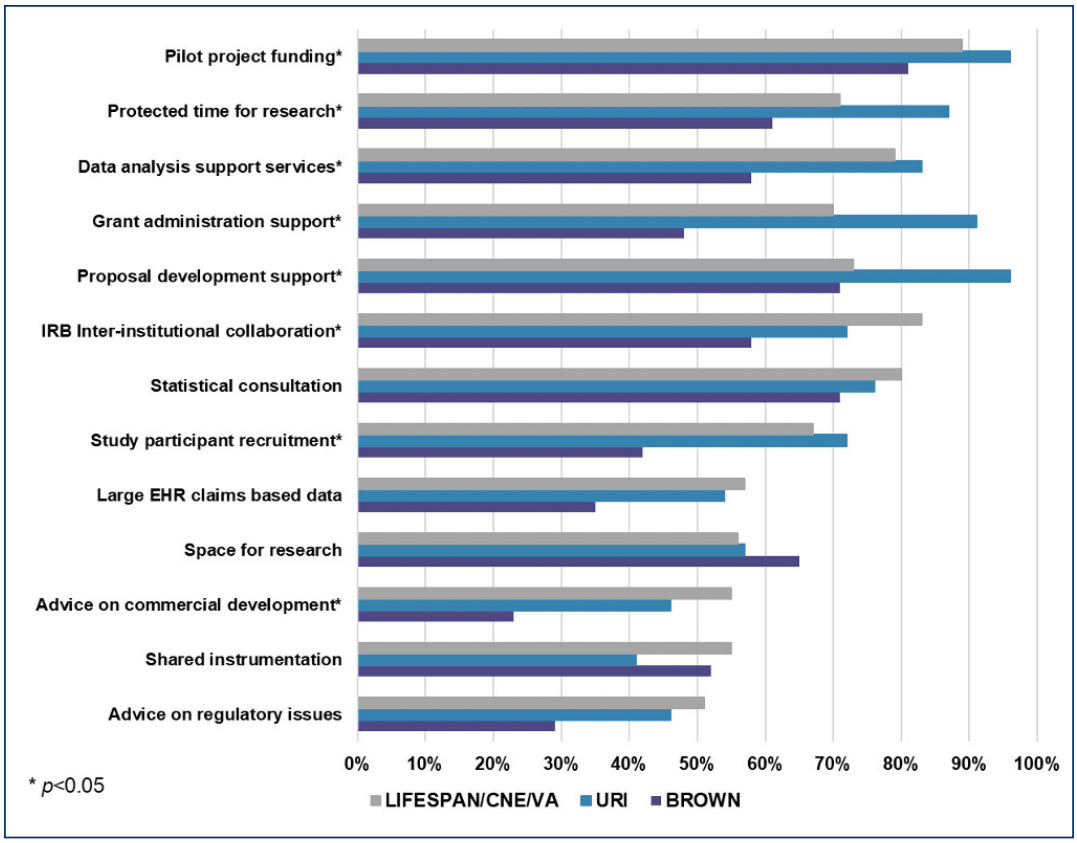

Figure 1. RI Investigator Needs Assessment Results (2017). Investigators (n = 171) indicated the most critical barriers to clinical and translational research. Respondents chose their primary affiliation from three options: Lifespan, Care New England or the VA Providence Healthcare System (Lifespan/CNE/VA; grey bars), University of Rhode Island (URI; blue bars), and Brown University (Brown; purple bars).

ADVANCE-CTR PARTNERS

The Advance-CTR partnership includes Brown University, the University of Rhode Island (URI), three academic health systems (Lifespan, Care New England, and VA Providence Healthcare System), and the RI Quality Institute (RIQI). These partners contribute expertise in biological, clinical, public health, pharmacy, nursing, population, and community-engaged research, and undergraduate, graduate, and professional school education. Combined, the three healthcare systems provide care to over 75% of the state's population, facilitating population-based and clinical research. RIQI is home to the state's health information exchange, CurrentCareTm. The RI Department of Health, RI Public Health Institute, and Brown University's Swearer Center also serve as key collaborators. The culture of collaboration across RI has been strengthened by the inter-institutional and intra-IDeA program cooperation across the Centers for Biomedical Research Excellence (COBRE), IDeA Network of Biomedical Research Excellence (INBRE), Environmental Influences on Child Health Outcome (ECHO) and CTR awards. This is reflected by open access to CTR resources, prioritization of services, recurring PI meetings, shared sponsorship of statewide symposia, and collaboration on newly identified initiatives to expand our network's capabilities.

ORGANIZATIONAL STRUCTURE

The organizational structure of Advance-CTR is shown in **Figure 2**. Oversight is provided by two support Cores: a centralized Administrative Core and a Tracking and Evaluation Core. Three Service Cores provide support to RI investigators: Clinical Research Design, Epidemiology, and Biostatistics; Biomedical Informatics and Cyberinfrastructure Enhancement; and Clinical Research Resources and Facilities. Advance-CTR's two Award Cores provide funding to foster new collaborations among early-career investigators new to clinical and translational research: Pilot Projects Program and Professional Development. Core Directors direct the implementation and progress of their respective cores, participate in Advance-CTR's Operations Committee, and coordinate inter-Core collaborations (**Table 1**). Core-specific Steering Committees provide the knowledge and experience necessary to offer guidance on initiatives and issues. In the Award Cores, these committees also provide crucial input as the "Study Section" for the application review process.

The Administrative Core provides centralized leadership, governance, financial management, organizational structure, and advisory support to develop, maintain, and enhance the Advance-CTR activities. The Administrative Core leads the development, coordination, and implementation of new strategic initiatives to enable highly efficient operational integration across the Cores. In addition to administering

Figure 2. Organizational Structure of Advance-CTR.
The two centralized Administrative and Tracking and Evaluation Cores (grey circles) support two Award Cores (blue circles) and three Service Cores (purple circles).

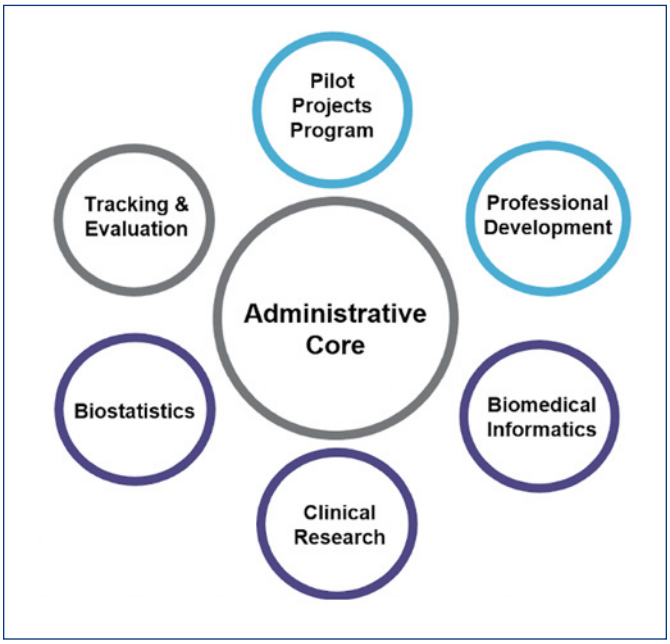

Table 1. Advance-CTR Core Directors

Name	Core	Home Institution
Elizabeth S. Chen, PhD, FACMI *Director*	Biomedical Informatics and Cyberinfrastructure Enhancement	Brown University
Christopher H. Schmid, PhD *Director*	Clinical Research Design, Epidemiology and Biostatistics	The School of Public Health, Brown University
Jason T. Machan, SCM, PhD *Co-Director*	Clinical Research Design, Epidemiology and Biostatistics	Rhode Island Hospital (Lifespan)
Bharat Ramratnam, MD *Director*	Clinical Research Resources and Facilities	Lifespan
Sharon Rounds, MD *Director*	Pilot Projects Program	Brown University
Michelle Lally, MD, MSc *Co-Director*	Pilot Projects Program	VA Providence Healthcare System
Ira B. Wilson, MD, MSc, FACP *Director*	Professional Development	The School of Public Health, Brown University
Stephen Kogut, PhD, MBA *Director*	Tracking and Evaluation	The College of Pharmacy, University of Rhode Island
Anthony Hayward, MD, PhD *Co-Director*	Tracking and Evaluation	Brown University

the business, financial, communication, and program management functions, this Core develops comprehensive written policies and standard operating procedures that support effective organization and governance. The Administrative Core fosters the growth and long-term sustainability of Advance-CTR to support clinical and translational research investigators' retention in RI.

The Tracking and Evaluation (T&E) Core supports tracking, evaluation, planning, needs assessment, and data dissemination. The T&E Core implements a participatory evaluation model that relies upon collaboration with Core directors in adapting evaluation plans to the evolving array of programs and services. Key Performance Indicators track output and outcome measures of CTR-related infrastructure, resources, and activity. The T&E Core monitors achievement of short- and long-term overall and specific Core goals and promotes quality improvement through outcomes-based feedback to the Operations Committee and each Core Director. The T&E Core led the statewide needs assessment and collection of baseline data addressing clinical and translational investigators' needs and created the focus for evaluation planning by stakeholder groups.[2] This was followed by a participatory Group Concept Mapping (GCM) study involving investigators and research administrators from each of the partner institutions to prioritize efforts to enhance the quality and quantity of clinical and translational research in RI.[3] Results of this statewide GCM study have been shared across the CTR/CTSA Evaluators collaborative and were presented at the 2018 meeting of the American Evaluation Association.[4] The T&E Core conducted a subsequent GCM study with Brown University's Swearer Center and its community partners to identify leading health priorities from the communities' perspective.

The Clinical Research Design, Epidemiology, and Biostatistics Core provides services, resources, education, mentoring, and tools to support clinical and translational research. Through their distributed "storefront model," the Core offers drop-in sessions and service consultations, resulting in >500 consultations to date to faculty at all career levels across our partner institutions. The Core supports investigators in study design, data collection, management, analysis, interpretation, and presentation using procedures that ensure quality control and reproducibility of analyses. They support a full range of quantitative, qualitative, survey, and mixed methods research designs. The Core has developed its seminar series, mini-symposia, and training materials in study design, epidemiology, and biostatistics for clinical investigators, and as well as training in statistical collaboration and consultation by Core statistical staff and student consultants. To increase

accessibility, all resources are available on the Advance-CTR website, shared broadly on the national IDeA-CTR website, CTRnet.org, and the DIAMOND™ web portal hosted by CLIC at the University of Rochester (https://clic-ctsa.org/diamond).

The Biomedical Informatics and Cyberinfrastructure Enhancement Core contributes to professional development in biomedical informatics through its consultation program, educational programs, workshops, and other engagement activities that enhance collaborative interactions within RI and across the IDeA network. The Core has implemented widely used standards-based tools, such as OHDSIOMOP and i2b2/SHRINE, to support multi-purpose cohort identification and studies using electronic health record (EHR) data from our affiliates. They enable widespread use of the state's designated health information exchange (HIE), CurrentCare™. The Core also secured access to the HealthFacts RI, an all-payer claims database (APCD) for clinical and translational research. They developed the first statewide instance of REDCap and directed an Advance-CTR award program to fund projects using Big Data. This Core will host the IDeA-CTR Network Biomedical Informatics Consortium's Coalition that builds collaborations across each of the CTR award programs on a national level.

The Clinical Research Resources and Facilities (CRC) Core provides services, resources, and professional development opportunities to support clinical and translational research. This Core is an easily accessible center that provides investigators with a space to perform study visits and trained Research Nurses and Coordinators to perform study measures and phlebotomy. The Core provides expertise in clinical trial study design and budget development, resources for biospecimen processing and storage, and support for IRB applications, particularly for junior investigators. The Core supports the education and certification of research personnel at each of our partner sites, including training for Good Clinical Practice (GCP) and Public Responsibility in Medicine and Research (PRIM&R), and professional certification in Clinical Research by the Society of Clinical Research Associates (SOCRA).

The Pilot Projects Program (PPP) Core addresses the identified statewide gaps in pilot funding to support clinical and translational research investigators to ultimately impact state health priorities. Special consideration is given to community-engaged projects that address health disparities and other research priorities. The PPP Core has significantly enhanced the quality and quantity of clinical and translational research in RI by awarding 33 Pilot Projects spanning the T0 to T4 research spectrum and by developing multi-disciplinary research collaborations among co-PIs across the state. This Core has received proposals from 454 unique applicants across our statewide consortium. The 59 awarded investigators have subsequently received 26 independent, extramural awards. The PPP Core coordinates the annual statewide Emerging Areas of Research Symposia, which brings together all RI IDeA program staff and faculty.

The Professional Development (PD) Core offers training opportunities that promote the career development of clinical and translational research investigators. These opportunities include a monthly trans-institutional seminar series where investigators present their research-in-progress and receive feedback from peers and Advance-CTR leadership. A two-year Mentored Research Award program has funded 11 scholars, and to date, 10 have received extramural funding. This Core provides partner-wide, web-based training in interdisciplinary clinical and translational research-oriented topics (e.g., team science), and in-person and web-based training focused on the commercialization of research findings. The PD Core sponsored faculty from each of our partner organizations to become qualified to implement the evidence-based curriculum for mentor training developed by the National Research Mentor Network (NRMN) and the Center for the Improvement of the Mentored Experience (CIMER). To date, 8 trainers have applied this curriculum to train 105 RI faculty to become more effective research mentors to junior faculty. In partnership with the Brown Division of BioMed, the PD Core supported Advance-K's creation, a formally structured, year-long, intensive program to guide selected early-career faculty to prepare and submit individual career development awards. This program was formed specifically to address the challenges of clinician scientists' ability to secure release time and obtain the mentorship needed to develop career development plans and awards.

LEADERSHIP AND SHARED GOVERNANCE

The PD/PI of Advance-CTR and the chair of the Operations Committee is James Padbury, MD. With Program Coordinator Edward Hawrot, PhD, he co-leads a centralized Administrative Core that provides an integrated and efficient structure for program management. The Administrative Core includes a Director and a dedicated Manager for the Award Cores, the Service Cores, Communications, and Data Management. This administrative structure provides close integration across the multi-institutional Cores, assurance of best practices with and between administrative functions, and balance across our network of partners. Advance-CTR is advised by highly engaged Operations, Steering, Internal, and External Advisory Committees, with oversight and guidance provided by key stakeholders from our partner sites. The leadership approach is based on institutional integration and balance, representing every stakeholder in our network. The Operations Committee oversees Core management and productivity; allocation of resources, educational initiatives, and training programs; supports projects at individual institutions; contributes to building and space decisions, the distribution of infrastructure resources, and decision-making

for program evaluation. The Steering Committee assures accountability for operations, coordination, resource management, data tracking, and program effectiveness across the Advance-CTR partner institutions. The Internal Advisory Committee includes leaders from partner institutions and community representatives who contribute to the strategic vision and allocation of Advance-CTR resources. The External Advisory Committee advises Advance-CTR leadership, providing formal recommendations and support.

HIGHLIGHTS AND ACCOMPLISHMENTS

In response to investigator needs and keeping with the health priorities of RI, Advance-CTR funded 53 awards to projects that span the translational research spectrum. Funded projects address top RI health concerns, including mental health disorders among adults, children, and adolescents, and research on opioid use at the individual, patient, and community level. Advance-CTR gives priority consideration to projects that address community health priorities, are conducted in communities, and employ community partners. Awarded research has utilized computational approaches across various areas: in health services, analytical decision support, and machine learning approaches to sophisticated diagnostic algorithms. In the past 4.5 years, 42 investigators supported by Advance-CTR (awardees and direct service users) have generated 61 extramural grants totaling $14.3M for a return on investment of 3 to 1. Additionally, Advance-CTR Core Directors and investigators have received supplemental awards for Alzheimer's Disease Risk Assessment, participation in the N3C CTSA/CTR COVID-19 Data Registry, and in the RADx-UP consortium.

The Service Cores continue to meet investigators' needs through complimentary service consultations, original seminars and symposia, and resource creation. There is a particularly high demand for consultations in biostatistics, research design, and qualitative methods. In response, the Biostatistics Core has provided 639 consultations to 295 unique investigators as of December 31, 2020. Likewise, the Cores have provided individual and group training for NVivo qualitative software, which was previously unavailable on a statewide level, as well as consults for survey creation, design, and analysis. The Biostatistics and Biomedical Informatics Cores have led a joint effort to provide REDCap assistance to investigators. In contrast, the CRC Core has supported costly clinical research certification training to administrators at its hospital partners. One of the most impactful services that Cores have provided is its matchmaking of early-career investigators with mentors and faculty experts at different institutions. The Service Cores have facilitated dozens of cross-institutional collaborations between investigators of diverse disciplines that have yielded extramural funding, publications, and ongoing partnerships.

SUMMARY

Advance-CTR leverages resources to establish clinical and translational programs that were either not previously available or siloed within single partners with a statewide consortium of partners. Notably, Advance-CTR introduced pilot, career development, and big data awards along with faculty development programs. Advance-CTR has created three consultative Service Cores, all of which were previously limited in availability at the statewide level. As a result, Advance-CTR serves as a research hub and training umbrella for the entire RI clinical and translation research investigator community. Advance-CTR aims to enhance patient-centered research and accelerate health discoveries that benefit RI's communities, and impact the state's leading health needs.

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