Health Research Nonformula Grants - State Fiscal Year 2010-11

Health research nonformula grants totaling $16,684,527 were awarded to four organizations in response to the Request for Application (RFA) # 09-07-05 for Collaborative Research on Substance Abuse. All research projects addressed the following research priority established by the Department in conjunction with the Health Research Advisory Committee:

> For the purpose of priority setting and funding, the Health Research Advisory Committee recommends combining the two nonformula funding categories of clinical and health services research and other research. The research priority shall involve collaborative research integrating efforts from several disciplines and institutions. The research priority for nonformula-funded research is:
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> Substance Abuse
> Research to understand the biological basis of addiction and the neural changes that can lead to addiction and to evaluate interventions to prevent and treat addictions. The research should focus primarily on addiction to illicit drugs, but should not exclude research on alcohol or tobacco use as co-morbidities to illicit drug use or research on polydrug use. Illicit drugs include, but are not limited to, marijuana or hashish, opium, heroin, cocaine (including crack), inhalants, hallucinogens (including phencyclidine [PCP], lysergic acid diethylamide [LSD], and Ecstasy [MDMA]), or prescription-type psychotherapeutics used nonmedically, which include stimulants, sedatives, tranquilizers, and pain relievers (including opioid analgesics). Opioid analgesics include methadone, other opioids such as oxycodone and hydrocodone, and synthetic narcotics such as fentanyl and propoxyphene.
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> Research may include, but is not limited to, the following areas:
> - Research to investigate why certain substances are addictive and what happens to cells in the brain to cause craving; which neural circuits, cells, and mediators in the brain are involved in substance abuse and how can they be modulated to break the cycle of addiction; how various substances of abuse affect brain cells, targets in the brain (receptors and transporters), communication between brain cells, and pathways that are important in behavior; how the brain changes with substance use, whether the effects are dose-dependent, when brain changes become irreversible, how brain changes alter behavior, and how people vary in their adaptive changes in brain function with substance use.
> - Research on the mechanisms of drug interactions and co-drug dependency, how multiple drugs interact with each other and the brain to potentiate each other in terms of addiction risk, and how this cycle can be "short-circuited."
> - Research on animal models to elucidate the functional brain impairments associated with substance use and addiction.
> - Research on the use of noninvasive brain imaging to identify brain regions and neural pathways that are differentially activated during drug addiction.
> - Research to determine whether potential therapeutics for the management of substance use disorders can be identified by their ability to alter addiction-associated patterns of brain activity.
> - Research on how host susceptibility, genetic factors, and environmental factors interact to contribute to addiction susceptibility, particularly early life environmental exposures and their effects on the brain.
> - Research on the genetic and epigenetic factors that influence life-time risk of substance abuse.

- Research on risk factors that influence the initiation of substance use, addiction to substances and relapse from substance abuse treatment.
- Research on the use of genetic and genomic information to tailor individualized approaches to substance abuse prevention and treatment.
- Research on the measurement of risks for and severity of addiction.
- Research on disorders and risky behaviors that co-occur with substance abuse disorders and how these co-morbidities can be managed effectively.
- Research on the genetic, neurological, social, and contextual factors that influence the effectiveness of programs aimed at preventing substance use and abuse in late adolescence and early adulthood.
- Research on the impact of a chronic, continuing care versus acute care addictions treatment model on the costs of treatment and health outcomes.
- Research to determine which program delivery approaches maximize program sustainability, barriers to the implementation of evidence-based practices, and how evidence-based practices can be implemented most effectively through all phases of prevention and treatment, including diagnosis, intervention, and long-term follow-up.
- Research on interventions for individuals for whom current approaches are ineffective.
- Research on the barriers to the implementation of substance abuse screening in primary care settings, effective approaches to expand screening for substance use disorders in health care settings, and tools and technologies to better identify which patients will respond to various types of treatment approaches for use in substance abuse screening.
- Research to determine the efficacy of new therapies to prevent or treat addiction. Testing of such interventions should include objective evidence of prevention or treatment in defined cohorts.

<u>Research in the following areas will not be considered:</u>

- Research focused primarily or exclusively on addictions other than illicit drugs. Research focused primarily or exclusively on gambling, addictive sexual behavior, obesity and food addiction, tobacco use and alcohol abuse will not be considered.
- Research on the benefits of any substance of abuse.
- Research on the abuse or misuse of antibiotics.

The research should hold the potential for addressing the health needs of underserved segments of the population, including rural, urban, racial/ethnic minorities, and other populations that are at high risk for substance abuse. To foster cross-institutional collaborative research among organizations across the Commonwealth, an applicant must conduct research in collaboration with other research institutions and organizations. To the extent possible, organizations that are not academic medical centers, such as smaller colleges and universities, businesses, biotechnology and pharmaceutical companies, health care providers and local public health agencies should be included in addition to major research institutions. At least two of the collaborators must be major research institutions. Collaboration with a minority-serving academic institution or a minority-serving community-based organization in Pennsylvania is strongly encouraged, and should include the mentoring and training of students. All research collaborators must play a substantive and meaningful role in multiple aspects of the proposed research. Research proposals must be organized around specific focused topics or issues rather than a wide range of unrelated projects. Health services research must include objective evidence of outcomes. Research must test at least one hypothesis, not be merely descriptive or hypothesis-generating.

At least 50 percent of each grant's funds must be spent on clinical and/or health services research as defined in Act 2001-77; no more than 50 percent of each grant's funds may be spent on biomedical research, as defined in Act 2001-77.

The following list of grant awards provides the lead and collaborating institutions, title of the research project, amount of the grant award, grant award period, contact principal investigator, co-principal investigators, project purpose, project overview and expected research benefits and outcomes.

Substance Abuse Research Projects

- The Pennsylvania State University and Lincoln University - *A Multidisciplinary Research Paradigm for Assessing and Guiding Addiction Treatment*, $2,191,427 for a 48-month project (June 1, 2011 — May 31, 2015)

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  Type of Research: Biomedical

  Project Purpose: The overall goal of our program is to develop a preclinical basic science model to study the dysregulated state (variously called allostasis or protracted abstinence) that predicts relapse in an opiate addicted subject and to test whether this state can be reversed following treatment with depot naltrexone. Depot naltrexone is a newly formulated drug that was recently approved for the treatment of opiate addiction in humans. It is our hope that these data will identify a complex of measures that indicate susceptibility to relapse and to treatment and, thereby inform the strategy employed for the diagnosis and treatment of addiction in humans.

  Project Overview: There are two broad research objectives: *1) To establish a rodent model of multisystem dysregulation that persists following opiate withdrawal and is believed to contribute to risk of relapse.* While neuroscientists have described abnormalities in hypothalamic pituitary adrenocortical (HPA) axis function, stress response, response to natural rewards and drug-related cues, as well as epigenetic changes associated with this state, they have not been studied in concert, and there are insufficient data on the duration or reversibility of these abnormalities over time or with medication. *2) To provide meaningful research experiences to minority undergraduate students through our summer research internship program, as well as the mentorship needed to help prepare these students for graduate training in biomedical research and/or medical school.*

  In the animal model studies, the specific aims are: *1) To track heroin-induced dysregulation of behavioral, physiological, neural, and genetic measures; 2) To determine whether and when depot naltrexone will reverse specific elements of systemic dysregulation; 3) To test whether depot naltrexone-associated normalization of these*

parameters will persist following a return to a drug-free state (i.e., following discontinuation of depot naltrexone treatment); and *4) To determine whether normalization of these parameters will shift the balance from drug-related to alternative natural rewards.*

Expected Research Outcomes and Benefits: This project has a number of expected outcomes. (1) The proposed studies will allow for the development of a sophisticated animal model that will use multiple measures to establish a profile of vulnerability vs. resilience in the face of addiction and, ultimately, in response to treatment. Evidence suggests that these indices translate nicely to the human condition and, as such, these preclinical data will serve to inform the diagnosis and treatment of addiction in the human population. (2) From a practical standpoint, depot naltrexone has a great deal of potential, but it also is very expensive (about $1,100/monthly injection). The present set of studies will be the first to examine the consequences of discontinued treatment. What happens when one comes off of the drug after a series of monthly treatments? (3) While depot naltrexone can be a very effective treatment, the literature suggests that about half of the subjects drop out of the treatment program. Might it be possible to increase compliance with the addition of alternative rewards? The present study will be the first to examine, using the animal model, whether the availability of an alternative reward will serve to increase the effectiveness of the drug. (4) While there is a great deal of overlap between the addictive state in humans and animals, some assessments simply cannot be made in the human population. The proposed studies in rodents, then, will enable us to explore variables (e.g., protein and gene expression in brain regions) that cannot be studied in patients and which may suggest new directions for medications development. (5) Our educational partnership with Lincoln University is designed to provide hands-on research experience and ongoing mentorship to young people to help to prepare them for graduate school or medical school. (6) Finally, our external advisory committee of distinguished basic and clinical scientists and Pennsylvania-based health policy makers will help to ensure the relevance of the research to the citizens of our state and proximal area.

- Treatment Research Institute, Family Practice and Counseling Network, Lincoln University, Public Health Management Corporation and University of Pennsylvania - *Integrating Substance Abuse Assessment and Intervention in Primary Care Settings*, $4,493,185 for a 48-month project (June 1, 2011 — May 31, 2015)

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  Type of Research: Clinical and Health Services

Project Purpose: The purpose of the proposed studies are to compare screening, brief intervention, and referral to treatment (SBIRT) to a screening protocol which features an expanded intervention (SBIRT+) for addressing substance use in primary care settings in underserved urban neighborhoods. We will implement SBIRT in three primary care centers, and conduct a randomized controlled trial comparing treatment engagement, substance use, and cost-effectiveness outcomes between SBIRT and SBIRT+ for 600 randomly assigned patients who will be followed over 12 months. The proposal features implementation and sustainability evaluations. Completion of this project will enable our team to conclude whether expanded brief intervention is more effective than a standard SBIRT protocol, and whether this expanded intervention is sustainable and cost-effective.

Project Overview: The broad research objectives of this project are to assess the effectiveness and sustainability of a model of behavioral health integration directly into primary care. This model targets screening, expanded brief intervention, and ongoing monitoring of substance users, and will address significant gaps in scientific understanding of the broad effectiveness of brief intervention for substance use in primary care settings.

Specific Aim 1- To implement a high fidelity SBIRT protocol with computerized screening technology into three primary care clinics in urban Philadelphia, and to train three behavioral health counselors in an expanded brief intervention protocol (SBIRT+); *Specific Aim 2*- To conduct a randomized controlled trial to assess whether patients assigned to receive SBIRT+ will attend more substance intervention and treatment sessions, demonstrate greater improvements in drug use, and demonstrate improved medical, employment, legal, and psychiatric function as well as reduced HIV risk behaviors than patients assigned to SBIRT. This trial will also address whether the introduction of SBIRT and SBIRT+ in primary care clinics is cost-effective relative to societal costs; *Specific Aim 3* - To determine whether SBIRT and SBIRT+ are sustainable in primary care clinics as research funding for behavioral health counselors is phased out in Year 4 of the project; *Specific Aim 4*- To conduct a process evaluation of SBIRT+ at the three collaborating clinics consisting of focus groups, structured interviews to assess implementation barriers and workforce attitudinal shifts to help inform methods to further disseminate SBIRT or SBIRT+, should the trial prove it is sustainable and cost-effective; *Specific Aim 5*- To provide a clinical research training environment for graduates and undergraduates from Lincoln University; this training experience will balance hands-on clinical data collection and didactic training.

After implementing SBIRT as standard practice in three multi-provider primary care clinics which operate in underserved neighborhoods in Philadelphia and training behavioral health consultants in the provision of an expanded version of SBIRT that incorporates ongoing monitoring, we will randomly assign 600 patients to receive: 1) one session of brief intervention (SBIRT) or 2) 2-6 sessions of brief intervention with ongoing telephone monitoring (SBIRT+). Patients will be followed-up every 3 months for 12 months with a multi-dimensional assessment and biological verification of drug use. We will conduct an implementation process evaluation, a sustainability evaluation at study end, and a cost-effectiveness evaluation of the two interventions.

Expected Research Outcomes and Benefits: *Health Benefit Gains*: Individuals who abuse illicit substances comprise a vulnerable population, as they are at greater risk of contracting HIV, experiencing chronic medical conditions and early mortality. The participants in this research, and by extension, the non-participants at the collaborating clinics in which this project is hosted, will be exposed to an intervention which should

reduce illicit substance use, promote greater treatment engagement in specialty care, and improve their general medical outcomes.
Scientific Knowledge Gains: This project will address a gap in the scientific literature regarding a model of behavioral health integration that has been shown to effectively address alcohol abuse, but has not been rigorously studied in the case of illicit drug use. The research project is powered to detect potential differential effects of two interventions on harder illicit drug users (such as heroin and cocaine users) compared to primary marijuana users and primary alcohol users. The research project will improve implementation knowledge, and will include a robust assessment of the intervention's cost-effectiveness and sustainability.
Collaborative Gains: This project will provide a vehicle to foster a growing collaborative relationship between scientists at the Treatment Research Institute (TRI) and the University of Pennsylvania with scientist-practitioners from the Public Health Management Corporation, Drexel University Health Services, and the Family Practice and Counseling Network in Federally Qualified Healthcare Center settings. These relationships will provide bi-directional knowledge transfer, as scientists from TRI will be able to share broad behavioral health treatment knowledge with the primary care providers, and the providers will be able to shape future research efforts; we envision future and ongoing collaborative projects and grant applications.
Educational Gains: Students from Lincoln University will experience a broad and enriching internship in health systems and clinical research that will lead many of them to pursue careers in health research.

- University of Pennsylvania, Lincoln University and Philadelphia VA Medical Center - *CURE Addiction Center of Excellence: Brain Mechanisms of Relapse and Recovery*, $4,999,999 for a 48-month project (June 1, 2011 — May 31, 2015)

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  Type of Research: Clinical

  Project Purpose: The overall purpose of the proposed project, a "CURE Addiction Center of Excellence: Brain Mechanisms of Relapse and Recovery", is to develop an understanding of the biological mechanisms of relapse that may be common across drugs of abuse – knowledge that is lacking, but critical for changing the harsh relapse statistics for addiction (up to 80% of treated individuals have relapsed by 6 months following treatment). The expected scientific yield is a brain-based understanding of relapse vulnerability that will enable targeted, novel (medication and behavioral) interventions to improve the health of addicted Pennsylvanians, save billions in addiction-related costs, and offer new hope for recovery to all those afflicted with these painful disorders.

Project Overview: The extraordinary cost of addiction – financially, medically and socially – is directly related to the stubborn clinical problem of relapse. The striking similarity of relapse rates across a wide range of addictive drugs, demographics, and treatments suggests shared biologic vulnerabilities that, if understood, could offer new treatment targets -- saving billions in addiction-related costs, and offering dramatically improved odds for recovery from addiction. This critical knowledge is lacking, but rapid advances in the clinical neuroscience of addiction have put it within our reach.

Understanding the biological mechanisms of relapse shared by drugs of abuse is thus the over-arching goal of our CURE project. The expected scientific yield is a brain-based understanding of relapse vulnerability – generating treatments that will permanently alter the harsh relapse statistics for addiction.

The proposed CURE Addiction Center of Excellence will use functional magnetic resonance imaging (fMRI) and specific probes of reward and inhibition as biomarkers predicting drug use during (Aim 1) and after (Aim 2) treatment in 216 patients addicted to cocaine (Component 1), marijuana (Component 2), and prescription opioids (Component 3). Participants will be scanned before, during, and after a 12-week active treatment specific to each of these drugs of abuse. The brain fMRI measures will be correlated with the primary clinical outcome of drug use (by urine drug screen) during the treatment and follow-up phase. Exploratory Aim 3 will examine the impact of genetic (e.g., polymorphisms modulating reward and inhibition) and epigenetic factors (e.g., history of prior trauma/abuse) on the relapse-relevant brain measures. The Minority Training Aim 4 will offer mentored research internships within the CURE projects to selected Lincoln University undergraduates.

The proposal reflects an integrated collaborative effort between the University of Pennsylvania School of Medicine, Philadelphia Department of Veteran's Affairs Medical Center, Lincoln University, and two community addiction treatment organizations, with guidance from (internal and external) Scientific Advisors and from Community Advisors in organizations supporting the recovery of addicted individuals (The Philadelphia Alliance, PROACT, Re-Enter, Gaudenzia, and PeerStar).

Expected Research Outcomes and Benefits: The field of human addiction neuroscience has advanced rapidly in the past decade, often using brain imaging to identify a number of ways in which the brains of addicted individuals differ - in function or even in structure - from the non-addicted. What has not been determined is which (or whether) these many "brain differences" may explain the most painful feature of addiction: relapse. *This knowledge is critical for changing the harsh statistics of relapse (nearly 80% relapse by 6 months after treatment), and for reducing the enormous health, social and economic toll of addiction.*

The field has lagged in attempting to connect brain-imaging findings to clinical outcomes. There are a few hundred (by now) brain imaging studies in addiction, and also a few hundred clinical trials of various interventions (behavioral and pharmacologic), but the two efforts have not been joined on a scale that would offer stable, replicable results to guide new treatments. Unfortunately, this "separate but parallel" approach severely limits the scientific yield from both arenas: the clinical significance of the brain findings is indeterminate, and the clinical trials are uninformed by brain science that could provide new targets, or help match patients to existing treatments.

Our CURE project will provide the first large scale effort, in the nation, to link brain measures with drug use outcomes in a large cohort of underserved individuals receiving well-characterized treatments for addiction. *The expected scientific yield is a brain-based understanding of relapse vulnerability – an understanding that may provide a sea-change in addiction treatment, and permanently alter the dark relapse statistics for addiction*. These benefits would extend beyond our immediate community, to the Commonwealth, and to the nation.

- University of Pittsburgh, Carnegie Mellon University and the RAND Corporation - *Reducing the Cognitive Consequences of Cannabis Use by Adolescents*, $4,999,916 for a 48-month project (June 1, 2011 — May 31, 2015)

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  Type of Research: Biomedical, Clinical and Health Services

  Project Purpose: Use of marijuana and other forms of cannabis is increasing in young adolescents. Convergent lines of evidence suggest that cannabis use impairs cognitive abilities, but proof of cause-and-effect, and the brain mechanisms that explain this association, are lacking. In this project we propose a set of integrated aims, employing innovative and complementary research strategies, to test a single hypothesis that onset of cannabis use before age 16 alters the developmental trajectory of neural circuits that are critical for the normal maturation of core cognitive abilities. We will also examine the feasibility of preventive interventions to reduce cannabis in a high-risk population of 12 year olds, and conduct a research training program to engage under-represented minorities and other undergraduates in basic, clinical and health services research on substance abuse.

  Project Overview: Cannabis is the most widely used illicit drug in the United States. In 2009, the number of 12-17 year olds who reported using marijuana *increased* by ~10%, and the proportion of this age group who thought smoking marijuana carried a great risk of harm *declined*. Prolonged cannabis use has been associated with cognitive impairments. However, whether cognitive impairments persist after cessation of cannabis use, and whether these impairments are more pronounced and persistent in individuals who start using cannabis during adolescence when cognitive abilities are still maturing, remain unknown. To address these questions, it is critical to understand the impact of cannabis use on working memory (WM), a core cognitive process that matures during adolescence and is dependent on the development of the dorsolateral prefrontal cortex (DLPFC).

Based on existing literature, we propose in this project that an early age (before age 16) of onset of cannabis use (EAOC) disrupts the normal developmental trajectories of DLPFC circuits mediating WM, resulting in persistent WM impairments. However, the existing data that support this idea have several limitations. First, evidence of the long-term cognitive consequences of cannabis use in humans is limited by insufficient information about cognitive capacity prior to the onset of cannabis use. Second, no prospective studies have used assessments of WM and brain function with the sensitivity required to clearly demonstrate adverse effects of EAOC. Third, demonstrating causality requires experimental evidence of a biological mechanism that links age-related cannabis exposure with WM dysfunction.

We propose a set of integrated aims to test the central hypothesis that EAOC alters the developmental trajectory of neural circuits in the DLPFC, resulting in persistent impairments in WM function. Aim 1 examines the direction of the association between EOAC and cognitive function in epidemiological samples. Aim 2 assesses the neural substrates for the short- and long-term effects of EAOC on WM in a subset of subjects studied by Aim 1. Aim 3 directly tests THC as a causal agent of WM impairment and DLPFC circuitry dysfunction in a non-human primate model system using the same measures employed in Aim 2. Aim 4 uses health services research methods in a cohort of 12 year olds recruited by Aim 1 to explore novel strategies for preventing EAOC. Aim 5 seeks to train the next generation of substance abuse researchers, focusing on under-represented minorities, by engaging talented undergraduates in the research conducted in Aims 1-4.

Expected Research Outcomes and Benefits: The proposed studies will provide answers to the following questions that are essential for protecting the health and long-term well-being of young Pennsylvanians and for guiding legislation and public policy in substance abuse. Aim 1 will determine the risk and protective factors for EAOC. In addition, by controlling for cognitive capacity and psychiatric symptoms prior to the initiation of cannabis use, this aim will robustly reveal the strength and directionality of the association between EAOC, cognitive functioning, and symptoms of psychosis. Aim 2 will reveal the short- and long-term effects of EAOC on WM, a core cognitive process, and document the neural mechanisms that mediate these effects. By using both a cross-sectional design in young adults and a longitudinal design in 12 year olds, the results will reveal the magnitude, dose-response relationship, and persistence of the effects of EAOC on WM and brain function. Aim 3 will provide a critical test of the cause-effect relationship between cannabis use during adolescence and WM dysfunction, and reveal how cannabis alters brain development to impair WM. Aim 4 will demonstrate the feasibility of a method for implementing a computer-assisted decision support system that provides pediatricians with the resources to conduct assessments of risk for EAOC with adolescents and their parents, provide families with brief interventions to facilitate adherence to recommendations, and identify local treatment referral options tailored to individual family members. Aim 5 will deliver an effective program for engaging talented under-represented minority and other undergraduate students in research activities designed to recruit and prepare them for a career in substance abuse research. In concert, the findings from these studies will provide critical and robust knowledge about the risk and cognitive consequences of EAOC that is currently lacking, and if our hypotheses are supported by the new data, will provide a compelling rationale for a new strategy to prevent or delay the onset of, and thus reduce the cognitive consequences of, cannabis use by adolescents.