

# **Pennsylvania State University**

## **Annual Progress Report: 2010 Nonformula Grant**

### **Reporting Period:**

June 1, 2011 – June 30, 2011

### **Nonformula Grant Overview**

The Pennsylvania State University received \$2,191,427 in nonformula funds for the grant award period June 1, 2011 through May 31, 2015. Accomplishments for the reporting period are described below.

### **Research Project: Project Title and Purpose**

*A Multidisciplinary Research Paradigm for Assessing and Guiding Addiction Treatment* - 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.

### **Anticipated Duration of Project**

6/1/2011 – 5/31/2015

### **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.*

### **Principal Investigator**

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### **Other Participating Researchers**

Robert Bonneau, PhD, Loren Evey, PhD, Jidong Fang, PhD, Willard Freeman, PhD, Robert Levenson, PhD - all employed at Pennsylvania State University

### **Expected 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.

## **Summary of Research Completed**

Given that the grant started June 1<sup>st</sup>, 2011, no work has been completed on the grant as of June 30, 2011. We have, however, placed an order for our experimental chambers.