

Temple University

Annual Progress Report: 2006 Formula Grant

Reporting Period

July 1, 2010 – December 31, 2010

Formula Grant Overview

The Temple University received \$1,839,493 in formula funds for the grant award period January 1, 2007 through December 31, 2010. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Fracture Healing in Traumatic Head and Spinal Cord Injury: Role of Cannabinoids and Opioids
Nearly 10% of skeletal fractures do not heal and become nonunions. Nonunion fractures often require surgical or nonsurgical intervention to be repaired. Many clinical studies have shown enhanced osteogenesis in patients sustaining traumatic brain injury (TBI) or spinal cord injury (SCI), with accelerated fracture healing and heterotopic ossifications being common phenomena in these patients. Recent studies have shown that the neuroendocrine systems particularly, the cannabinoid and opioid systems, have agonistic and antagonistic effects on bone remodeling and in the regulation of bone formation/resorption. The project hypothesis is that endogenous cannabinoids and opioids play a crucial role in regulating fracture healing and osteogenesis following TBI and SCI.

Duration of Project

7/1/2007 - 6/30/2008

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement Annual C.U.R.E. Reports on the Department's Tobacco Settlement/Act 77 web page at <http://www.health.state.pa.us/cure>.

Research Project 2: Project Title and Purpose

Targeted Nanoconjugates for Intracellular Cancer Therapy - Killing cancer cells while sparing normal healthy cells has been a long-sought goal in cancer treatment. The goal of this project is to devise a cancer therapeutic drug which can be administered to patients by infusion into the bloodstream. The new drug would have several features: it would home in on cancer cells and bind to them; after binding it would enter the cancer cells; and once inside the cells a therapeutic agent would kill the cell. The therapeutic agent is designed to have no effect on normal cells,

because it is specific for the cancer cell. The core of the new drug will consist of tiny particles (about 1/100 the size of a red blood cell) to which the targeting and therapeutic components are bound, and which can be detected by imaging to track them in the body. The purpose of this project is to construct and test this targeted drug approach.

Duration of Project

7/1/2007 - 6/30/2009

Summary of Research Completed

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Research Project 3: Project Title and Purpose

Chemokine Interactions with Dopamine Systems in the Brain - Chemokines are a class of chemicals known to participate in the immune system. Recently, chemokines have been identified in brain cells, but their function in the brain is not understood. The overall goal of this project is to characterize the function of central nervous system chemokines and determine how they interact with other neurotransmitter systems, such as dopamine. A second goal is to study this interaction in a setting of drug abuse as our preliminary data demonstrate a significant interaction between chemokines and cocaine. Understanding the role of chemokines and their receptors in the behavioral effects of psychostimulants may ultimately lead to a novel therapeutic approach to treating cocaine and/or methamphetamine addiction, in addition to movement disorders involving central dopamine systems such as Parkinson's disease.

Duration of Project

7/1/2007 - 6/30/2009

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement Annual C.U.R.E. Reports on the Department's Tobacco Settlement/Act 77 web page at <http://www.health.state.pa.us/cure>.

Research Project 4: Project Title and Purpose

Leptin Agonist and Antagonist Peptides - Obesity has been identified as a risk factor for the development of approximately 30 different diseases and disorders, including cancer. There are currently no cancer therapeutics tailored for the obese population. In this project two accomplished investigators combine their experience in obesity-related cancer and drug design to develop peptide-based pharmaceuticals targeting leptin, a carcinogenic hormone produced by fat tissue.

Duration of Project

7/1/2007 - 6/30/2009

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement Annual C.U.R.E. Reports on the Department's Tobacco Settlement/Act 77 web page at <http://www.health.state.pa.us/cure>.

Research Project 5: Project Title and Purpose

Evaluating Sex Differences in Biomarkers of Inflammation of Cardiovascular Risk - The purpose of this research is to understand how gender differences are manifested in cardiac vascular risk. More specifically, are the current clinical risk assessment tools sufficient for therapeutic recommendations? Our hypothesis is that the state of inflammation in cardiac tissues from a variety of metabolic factors and disease provides a more reliable risk assessment tool. Therefore, analytical tools to quantitatively assess the levels of inflammation will be developed; and these methods will be applied to understanding the development of cardiovascular disease and related gender differences using a rat model.

Duration of Project

7/1/2007 - 6/30/2008

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement Annual C.U.R.E. Reports on the Department's Tobacco Settlement/Act 77 web page at <http://www.health.state.pa.us/cure>.

Research Project 6: Project Title and Purpose

Inhibition of HIV Biogenesis by TULA, A UBA-Containing, Ubiquitin-Binding Protein - In spite of considerable progress, HIV infection and AIDS are still a great threat to human health. Further progress in creating anti-HIV drugs is hindered by several peculiarities of HIV. One such peculiarity is the very high mutation rate of HIV proteins; they constantly change their “molecular signatures” - slightly enough to remain fully functional, but sufficiently to evade drugs and natural immune responses of the infected organism. However, HIV uses multiple proteins of the infected cells for its replication. Therefore, anti-HIV drug development focuses now on the cellular proteins involved in HIV replication. We have recently discovered TULA (T-cell ubiquitin ligand), a novel protein inhibiting HIV production. This project will be focused on understanding how TULA suppresses HIV and on establishing practical approaches for making TULA-based anti-HIV drugs.

Duration of Project

7/1/2007 - 6/30/2009

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement Annual C.U.R.E. Reports on the Department's Tobacco Settlement/Act 77 web page at <http://www.health.state.pa.us/cure>.

Research Project 7: Project Title and Purpose

Effects of Estrogen on GEC1 and K Opioid Receptor Levels in Vivo - Studies in humans and animals have shown that females have enhanced analgesic or anti-nociceptive responses to kappa opioid receptor (KOR) agonists than males. The purpose of the project is to examine whether estrogen up-regulates GEC1 and the kappa opioid receptor. GEC1 is a 117-amino acid microtubules-interacting protein. Recently we have found that GEC1 is associated directly with the KOR and expression of GEC1 enhances cell-surface and total KOR in vitro. It has been reported that estrogen up-regulates GEC1 mRNA in vitro and in vivo. We propose to examine whether estrogen enhances protein levels of GEC1 and KOR in vivo.

Duration of Project

7/1/2007 – 6/30/2008

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement Annual C.U.R.E. Reports on the Department's Tobacco Settlement/Act 77 web page at <http://www.health.state.pa.us/cure>.

Research Project 8: Project Title and Purpose

Role of Metabolizing Enzymes in Efficacy of Prokinetic Agents in Gastroparesis - Gastroparesis is a gastrointestinal motility disorder with poorly understood etiology. Drugs used to treat gastroparesis are metabolized by liver enzymes. The purpose of this project is to identify the specific enzymes that metabolize and inactivate these drugs. Patients refractory to single drug therapy are given multiple drugs in combination. This project will study potential drug-drug interactions based on common enzyme pathways. Finally, the genetic make-up of gastroparesis patients may play a role in drug efficacy. This project will identify and evaluate genetic differences in drug-metabolizing enzymes relevant to gastroparesis. Thus, the project will aim at understanding the metabolism of gastroparesis drugs, drug interactions, and role of variable genetics in therapy among gastroparesis patient populations.

Duration of Project

7/1/2007 - 9/30/2008

Summary of Research Completed

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Research Project 9: Project Title and Purpose

Development of a Bone Lengthening Device for Children - The purpose of the project is to develop a prototype of a bone lengthening device for children who have limb length discrepancy (LLD). Two internal fixator concepts are investigated. In the first concept, the lengthening is achieved using a remotely activated, motorized lead-screw actuation system. The device will be completely buried inside the body but mounted outside of the bone. In the second concept, the motorized lead-screw actuation system will be replaced by a magnetic smart memory alloy actuation system. The feasibility of the two concepts is currently studied in the Temple University's Composites Laboratory and the Philadelphia Shriners Hospital for Children.

Duration of Project

7/1/2007 – 6/30/2008

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement C.U.R.E. Annual Reports on the Department's Tobacco Settlement/Act 77 web page at <http://www.health.state.pa.us/cure>.

Research Project 10: Project Title and Purpose

The Role of TIM Molecules in Murine Mercury-Induced Autoimmunity - It is a newly learned concept that T-cell Ig-mucin (TIM) molecules play a role in modulating the immune system. This includes situations in which the immune system turns against its own body (autoimmunity), such as during Lupus, Rheumatoid Arthritis and Multiple Sclerosis. This project will aim to further classify the role of TIM molecules in autoimmunity, in order to define targets which may be acted upon to alleviate disease processes.

Duration of Project

7/1/2007 – 4/30/2009

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement Annual C.U.R.E. Reports on the Department's Tobacco Settlement/Act 77 web page at <http://www.health.state.pa.us/cure>.

Research Project 11: Project Title and Purpose

Effect of c-Cbl on Glioblastoma Motility - Many brain tumors are highly invasive and therefore extremely difficult to treat. Cells from the primary tumor often infiltrate into surrounding brain tissues, so that removal of the main tumor mass is not sufficient to prevent recurrence. Therefore, it is very important to understand the properties of brain tumor cells that cause them to migrate. This understanding should help us to develop the tools that reduce the migration rate of brain tumor cells. Glioma is the most common type of brain tumor. We have recently shown that c-Cbl protein has a strong inhibitory effect on the migration of glioma cells. This project will be focused on determining the mechanism(s) by which c-Cbl regulates migration of glioma cells with the ultimate purpose of using this knowledge to develop new drugs/therapeutic methods to treat brain tumors.

Duration of Project

7/1/2007 - 12/31/2008

Summary of Research Completed

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Research Project 12: Project Title and Purpose

Structural and Functional Importance of Sterol Superlattices in Membranes - The ultimate goal of this research is to understand the etiology of cholesterol-related biomedical problems. Cholesterol has been linked to many diseases, including atherosclerosis, hypertension, and diabetes. Previous studies on cholesterol-related diseases were mainly focused on blood cholesterol. This research attempts to demonstrate, eventually, that cholesterol in cell membranes is also bio-medically important. The short-term goal is to reveal a novel biophysical principle, that is, that cholesterol content in membranes serves as a bio-switch turning on or off membrane activities, including the activities of membrane enzymes and channels.

Duration of Project

7/1/2007 - 6/30/2009

Summary of Research Completed

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Research Project 13: Project Title and Purpose

A Role of Non Genomic Estrogen Receptor GPR30 in Cardiac Function - Cardiovascular disease is more prevalent in men and postmenopausal women compared with premenopausal women, suggesting gender differences in cardiovascular regulation. Estrogen is considered to be one of the protective factors. In addition to its beneficial effects on lipid metabolism and blood vessels, estrogen has been shown to have cardio-protective actions by increasing parasympathetic nervous tone to the heart. It is hypothesized that the newly discovered non-genomic estrogen receptor GPR30 plays a key role in regulating the heart rate. This hypothesis will be tested by complementary immunohistochemical, pharmacological, and in vivo approaches. By fully understanding the cellular and molecular mechanism underlying the cardio-protective action of estrogen, new therapies can be developed that will decrease the risks associated with gender-related health problems.

Duration of Project

7/1/2007 - 6/30/2008

Summary of Research Completed

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Research Project 14: Project Title and Purpose

Identification of MTBP Binding Proteins - The MTBP gene has recently been shown to play important roles in various proliferation control pathways and the protein is required for cancer formation. The mechanisms by which MTBP functions in these pathways are unknown. We plan to immunopurify MTBP interacting proteins, determine their identity and verify their interaction using alternative approaches. Successful identification of physiologically relevant MTBP binding proteins will provide essential clues of its molecular function.

Duration of Project

7/1/2007 - 6/30/2008

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the

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Research Project 15: Project Title and Purpose

Anti-Inflammatory and Anti-Restenotic Effects of Interleukin-19 - Cardiovascular disease is the number one killer of Americans. In vascular diseases, vascular smooth muscle cells (VSMC) migrate from the wall of the artery into the lumen of the vessel where they grow and synthesize inflammatory cytokines which occludes the artery. A great deal of attention has been given to the negative effects of pro-inflammatory cytokines in this process, but, little has been reported on the potential protective effects of anti-inflammatory cytokines on VSMC. We have novel preliminary data which shows that Interleukin-19 (IL-19) can prevent growth, migration, and expression of inflammatory genes in VSMC. The purpose of this project is to identify the molecular mechanisms whereby IL-19 inhibits expression of inflammatory genes in VSMC, which leads to reduced growth of those cells.

Duration of Project

7/1/2007 - 12/31/2008

Summary of Research Completed

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Research Project 16: Project Title and Purpose

Isolation and Characterization of Neural Progenitor Cells - Groups of morphologically distinct, small diameter cells, termed small intense fluorescent cells (SIF cells), exist in all known vertebral autonomic ganglia including human. There is evidence that SIF cells may represent neural progenitor cells. The goal of this project is to isolate, identify and characterize neural progenitor cells removed from sympathetic ganglia of the rat. Neural progenitor cells may be induced to differentiate into a specific phenotype by culturing in a defined medium or by mobilizing a specific intracellular calcium store. Differentiated neurons with defined phenotype may be grafted to a specific area of the brain or spinal cord to replace damaged neurons.

Duration of Project

7/1/2008 - 6/30/2009

Summary of Research Completed

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Research Project 17: Project Title and Purpose

The Molecular Requirements for TGF- β 1 Induction of CTGF Expression in Osteoblasts - Connective Tissue Growth Factor (CTGF) has recently emerged as an important growth factor in bone formation. We recently demonstrated that TGF- β 1 is a potent inducer of CTGF expression and that CTGF is a downstream mediator of TGF- β 1-induced extracellular matrix (ECM) production in osteoblasts. However, the mechanisms that control these TGF- β 1-induced CTGF mediated functions in osteoblasts are unknown. This project proposes to investigate the mechanisms whereby TGF- β 1 induces CTGF expression and to identify the signaling pathways that regulate CTGF mediated ECM synthesis.

Duration of Project

7/27/2007 – 6/30/2009

Summary of Research Completed

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Research Project 18: Project Title and Purpose

Analysis of the Human DDH1 Promoter in Cisplatin Resistant Ovarian Carcinoma Cells - Increased expression of Dihydrodiol dehydrogenase 1 (DDH1) protein has been demonstrated to induce cisplatin/carboplatin resistance in human ovarian carcinoma cells. The observed increase in protein expression was associated with the changes in the transcription of the DDH gene. This observation suggested that the promoter region of the DDH gene was essential in controlling its expression in the cisplatin-resistant cells. An approximately 3 kb region 5' to the ATG start site of the DDH gene has been identified to contain the elements that may be responsible for the increased expression of DDH1 in the cisplatin-resistant cells. This study aims to decipher the precise genetic elements and their associated transcription factor(s) that control the overexpression of DDH1 gene in the cisplatin resistant human ovarian cancer cells.

Duration of Project

7/27/2007 – 6/30/2008

Summary of Research Completed

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Research Project 19: Project Title and Purpose

Identification and Functional Importance of Src Family Kinases(SFKs) in Platelets - The main purpose of this study is to elucidate the role of Src family kinases (SFKs) in platelet activation and functional responses. Whereas multiple SFKs are expressed in platelets and are known to regulate key functional responses of platelets, the molecular basis of this underlying redundancy and whether these individual SFKs regulate distinct functions of platelets is incompletely understood. Here we propose to evaluate the functional role of SFKs upon platelet activation. The long-term goal of these studies is to assess whether SFKs or the pathways controlled by these important proteins would be targets for novel anti-thrombotic drugs.

Duration of Project

7/1/2008 – 6/30/2009

Summary of Research Completed

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Research Project 20: Project Title and Purpose

Perfluorochemical (PFC) Liquid-Assisted Ultrasound Imaging of the Lung - The purpose of this project is to use perfluorochemical liquids to increase the ultrasonographic visualization of the lungs in order to: 1) improve staging of lung cancer; 2) make endoscopic ultrasound guided fine needle aspiration (EUS FNA) possible in areas that are currently inaccessible; and 3) make ultrasonographic evaluation of the progression of the disease possible by measuring the volume of the tumor.

Duration of Project

7/27/2007 – 6/30/2010

Summary of Research Completed

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