

University of Pittsburgh

Annual Progress Report: 2007 Formula Grant

Reporting Period

July 1, 2010 – June 30, 2011

Formula Grant Overview

The University of Pittsburgh received \$8,868,580 in formula funds for the grant award period January 1, 2008 through December 31, 2011. Accomplishments for the reporting period are described below.

Research Infrastructure Project 1: Project Title and Purpose

Research Infrastructure: Biomedical Science Tower Chilled Water Plant Upgrade - The chilled water plant in the Thomas Starzl Biomedical Science Tower (BST) is necessary for normal operations of the research laboratories and animal facilities within the building. The existing chillers, cooling tower, and condenser piping were installed when the building was constructed in 1988 and have degraded to the point at which they require refurbishment or replacement. Because failure of the BST chilled water plant would be catastrophic to building operations, this project will provide upgrades to increase the plant's capacity, efficiency, and reliability.

Anticipated Duration of Project

7/1/2009 - 8/31/2011

Project Overview

The BST's existing chilled water plant dates to the building's construction in 1988. Many of the components have either degraded and must be refurbished or are far less efficient than newer machines and should be replaced.

The current cooling configuration includes seven chillers, providing 8,500 tons of cooling to produce chilled water for research and animal facilities throughout the BST. These machines are served by a 10,000-ton cooling tower located on the roof. Because the chilled water plant cannot be taken offline for repairs and improvements, the first stage of the upgrade will involve installation of a winter tower. Once it is installed, the main tower can be shut down, allowing it and the condenser piping to be refurbished. The winter tower will remain after the main tower goes back into service, providing additional condensing capacity to increase plant output and reduce energy consumption and costs during low-load conditions.

The York chillers are in relatively good shape but are far less efficient than newer models. In addition, they use R-11 refrigerant, which is expensive to replace and difficult to acquire, as it

has been phased out in response to environmental concerns and the Clean Air Act. Chiller upgrades will be accomplished by replacing two 1,000-ton York chillers with one 2,500-ton dual compressor machine that operates on both normal and emergency power. The new chiller is more efficient than the existing chillers and will increase the plant's output capacity by 500 tons. In addition, it will double the plant's cooling capacity during emergency power disruptions. To provide sufficient emergency power to the 2,500-ton Trane chiller and the new 2,500-ton dual compressor chiller during extended power disruptions, a new generator will be added to the chilled water plant. The cooling provided by these two units will be sufficient to maintain year-round building operations.

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None

Expected Research Outcomes and Benefits

This research infrastructure project will upgrade the BST chilled water plant. The upgrade will result in greater efficiency of the cooling units and reduced risk of system failure, which would be greatly detrimental to normal operations for the building's animal facilities and research laboratories. In addition, the upgrade will eliminate the need for R-11 refrigerant, which has been phased out by the Clean Air Act.

Summary of Research Completed

The piping installation process was completed in spring 2011, and all new equipment (chiller, cooling towers, pumps, emergency generator, etc.) has been installed and is operational. When the chilled water plant was back in full operation, we discovered that the existing chilled water flow meters, which ensure the proper operation of the entire chilled water system, were in very poor condition and needed to be replaced. The replacement of these flow meters will be completed in summer 2011, concluding this project.

Research Project 2: Project Title and Purpose

Organization of the Brain's Primary Motor Cortex and Premotor Areas - Concepts about the cortical control of movement have changed dramatically in recent years. In the past, the primary motor cortex (M1) was viewed as the sole source of spinal cord signals that produce movement. Subcortical areas, like the basal ganglia and cerebellum, were thought to mainly influence movement control through direct M1 connections. It is now known that the frontal lobe contains six premotor areas. Each of these cortical areas projects not only to M1, but also directly to the spinal cord, bringing to question the origin of central commands for movement. This project will examine: (1) how cortical neurons that influence individual muscles in the hand, arm, and shoulder are distributed in the cortical motor areas and (2) how the circuits that link the basal ganglia, cerebellum, and spinal cord with the cortical motor areas are organized.

Anticipated Duration of Project

1/1/2008 - 12/31/2011

Project Overview

This project is designed to answer two questions: (1) How are the cortical neurons that influence individual muscles in the hand, arm, and shoulder distributed in the cortical motor areas? (2) What is the organization of the circuits that link the basal ganglia, cerebellum, and other subcortical regions with the cortical motor areas? Across a series of experiments, the investigators will use transneuronal transport of neurotropic viruses, a technique that is unique in its ability to trace complicated circuits in the brain. Selected virus strains will be used to examine either the inputs to or the outputs from a site. By adjusting the survival time, circuits of varying levels of complexity can be studied.

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Expected Research Outcomes and Benefits

The results from these experiments are likely to have broad implications for understanding the function of the cortical motor areas in normal movement, their role in the recovery of motor

function following stroke or other neurotrauma, and their involvement in the generation of abnormal movements like those associated with Parkinson's disease.

Summary of Research Completed

Classically, the cerebellum is anatomically divided into three cortico-nuclear zones: a medial zone consisting of the cerebellar vermis and fastigial nucleus, an intermediate zone consisting of paravermal cortex and interposed nuclei, and a lateral zone consisting of the most lateral cerebellar cortex and the dentate nucleus. Each of these zones also is considered to be functionally distinct. For example, lesions of the vermis result in deficits in whole body posture and locomotion, whereas lesions of the lateral zone result in deficits in limb movements. Current texts include the vermis in the “spinocerebellum” and emphasize that it receives somatic sensory inputs related to the head and proximal parts of the body from ascending spinal pathways. In contrast, the lateral zone is included in the “cerebro-cerebellum” because it is densely interconnected with the cerebral cortex. We have begun to examine the inputs to the cerebellar cortex using retrograde transneuronal transport of rabies virus (RV).

METHODS. These data are based on observations from seven macaques (*Macaque mulatta* and *fascicularis*, 2.3–9.6 kg, three males and four females). In each monkey, we injected a mixture of RV and a conventional tracer (β -subunit of cholera toxin [CTb]) into selected lobules of the cerebellar vermis. We co-injected CTb with RV to facilitate identification of the injection site. The protocol for these experiments was approved by appropriate animal care and biosafety committees. Biosafety practices conformed to Biosafety Level 2 regulations outlined in “Biosafety in Microbiological and Biomedical Laboratories” (Department of Health and Human Services publication No. 93–8395).

All surgical procedures were performed under deep general anesthesia (1.5–2.5 percent isoflurane) and using aseptic conditions. Animals received dexamethasone (0.5 mg/kg, intramuscularly [i.m.]) the night prior to surgery. Respiratory rate, blood oxygen level, body temperature, venous blood gas, serum electrolytes, glucose, and sensitivity to noxious stimuli were monitored at regular intervals throughout the procedure.

Cerebellar vermis injections — Each animal's head was restrained in a Kopf stereotactic frame (Kopf Instruments), and a craniotomy exposed the posterior vermis and the paramedian lobules of the cerebellum. Prior structural magnetic resonance images (MRI) of each cerebellum enabled us to define the proper angle of approach and depth of injections into the vermis. A mixture of RV (N2c strain, 4.5×10^9 pfu/ml; provided by M. Schnell) and CTb (0.02 percent; List Biological Laboratories) was injected with a Hamilton syringe with a 30-gauge needle. Small amounts of the mixture (0.2 μ l) were injected at 0.5 mm intervals from 1 mm to as deep as 15 mm below the surface of the vermis. In six of the seven animals, we injected tracer at multiple locations in the posterior vermis by inserting the injection needle at six to eight sites. In one animal, we injected tracer at multiple locations in the posterior vermis by varying the angle of each needle penetration made at a single entry site. When we completed the injections, we covered the cerebellum with artificial dura, closed the incision in anatomical layers, and administered an analgesic (buprenorphine) and an antibiotic (ceftriaxone) at the appropriate intervals.

Prior studies have demonstrated that RV is transported exclusively in the retrograde direction in a time-dependent fashion. The time to infect first-, second-, and third-order neurons depends on the strain of RV and its concentration. Based on prior results, we set the survival time following the cerebellar injections to 42 hours. This interval is sufficient to allow transport of the N2c strain to second-, but not third-, order neurons.

At the end of the 42-hour survival time, the animals were deeply anesthetized using ketamine (25 mg/kg, intraperitoneally [i.p.]) followed by pentobarbital sodium (40 mg/kg, i.p.). They were perfused transcardially with 0.1 molar (M) phosphate buffer (pH 7.4), followed by 10 percent buffered formalin and a mixture of 10 percent buffered formalin and 10 percent glycerol at 4 degrees Celsius. The brain and spinal cord were removed from the skull and stored overnight in 10 percent buffered formalin and 10 percent glycerol at 4 degrees Celsius and then placed in 10 percent buffered formalin and 20 percent glycerol at 4 degrees Celsius for two weeks. Blocks of tissue (cerebral cortex, brainstem, and cerebellum) were individually frozen and sectioned at 50 μ m. Every 10th section was stained with cresyl violet for analysis of cytoarchitecture. Brain sections were immunohistochemically reacted according to the avidin-biotin peroxidase method (Vectastain; Vector Laboratories, Burlingame, CA). Alternating sections were reacted with mouse anti-M957 (supplied by Dr. Alex Wandeler, Animal Disease Research Institute, Ontario, Canada, 1:300) and goat anti-cholera toxin B subunit (List Biological Lab, Campbell, CA, 1:10,000) to detect RV or CTb, respectively. Reacted tissue sections were mounted on gelatin-coated glass slides, air dried, and coverslipped.

RESULTS. We injected a combination of RV and CTb into multiple posterior lobules of the cerebellar vermis. The tracer injections were made largely on or to the right of the cerebellar midline. Here we focus on the cortical neurons labeled in the left hemisphere.

The cerebral cortex projects to the vermis. Our major new observation was that retrograde transneuronal transport of RV from lobules IV-IXA of the vermis labeled large numbers of neurons in the cerebral cortex. The total number of neurons labeled in the cerebral cortex after retrograde transneuronal transport of virus from the vermis averaged 10,384 (measured on every fourth section, range 4,982-16,350, $n = 4$). In comparison, the total number of neurons labeled in the cerebral cortex after retrograde transneuronal transport of virus from comparable sized injections into the cerebellar hemisphere averaged 14,472 neurons (range 4,597-29,775, $n = 4$). The difference in these averages was not statistically significant (unpaired student's t-test). The density of labeled neurons in areas of the cerebral cortex following transneuronal transport of virus from the vermis also was comparable to that following transneuronal transport from the hemisphere. It has long been recognized that the cerebral cortex provides a major input to the hemisphere. Thus, our observations suggest that the cerebral cortex is a major source of input to the vermis.

The cortical motor areas are a source of input to lobules VB-VIII B. In two animals (M18, M19), the virus injection sites involved lobules VB-VIII B (M18: lobule VIIIA to VIII B; M19: lobules VB to VIIIA). In these animals, we found that the majority (74-88 percent) of the labeled neurons were located in the cortical motor areas in the frontal lobe. The cortical motor areas include M1 and the six premotor areas that project to it. Two of the premotor areas (PMd and

PMv) lie on the lateral surface of the hemisphere. Four of the premotor areas are located on the medial wall of the hemisphere; one of these is the supplementary motor area (SMA) on the superior frontal gyrus. The remaining three premotor areas are located in the cingulate sulcus, either rostrally (CMAr) or more caudally on the dorsal and ventral banks of the sulcus (CMAAd and CMAv).

In another two animals, the injection site extended either rostrally (M09) to involve portions of lobule IV and the intraculminate fissure (between lobules IV and V) or caudally (M84) to involve portions of lobule IXA. The cortical motor areas also contained labeled neurons in these animals. However, approximately half (42-58 percent) of the labeled neurons were located outside the motor areas. These observations imply that the cortical input to lobules VB-VIII B of the vermis originates mainly from the cortical motor areas.

Clearly, some of the cortical motor areas project more densely to lobules VB-VIII B than to others. Approximately half of the cortical neurons labeled following transport from lobules VB-VIII B were located in the premotor areas on the medial wall, especially in the SMA, CMAAd, and CMAv. In contrast, the density of labeled neurons in the two premotor areas on the lateral surface, the PMd and PMv, was relatively sparse. These two cortical areas combined contained 12 percent or less of the total number of labeled neurons. Thus, the three premotor areas on the medial wall appear to have a more prominent input to the vermis than the two premotor areas on the lateral surface.

Overall, the distribution of labeled neurons in the cortical motor areas varied with location of the injection site within lobules VB-VIII B. The density of labeling in the SMA, CMAAd, and CMAv was greatest in M18, the animal with the more caudally located injection site. On the other hand, the density of labeling in M1 was greatest in M19, the animal with the more rostrally-located injection site. Labeled neurons were relatively dense just caudal to the superior limb of the arcuate sulcus (ArS) in M18, whereas labeled neurons were sparse in this region in M19. These observations suggest that there is a degree of topography in the organization of projections from the cortical motor areas to different portions of lobules VB-VIII B.

In summary, we have made the surprising observation that M1 and several of the cortical motor areas on the medial wall of the hemisphere provide a major source of input to lobules VB-VIII B of the vermis. Furthermore, a substantial portion of this input comes from cortical regions involved in the control of distal as well as proximal limb movements. Thus, our results challenge the classical view of the vermis and indicate that it should no longer be considered as entirely isolated from the cerebral cortex. Instead, lobules VB-VIII B represent a site where the cortical motor areas can influence descending control systems involved in the regulation of whole body posture and locomotion. Whether additional areas of the cerebral cortex, including non-motor areas in the frontal lobe, influence the function of other regions of the vermis remains to be determined.

The cerebellar vermis is a target of the cortical motor areas. Keith A. Coffman, Richard P. Dum, Peter L. Strick. Proceedings of the National Academy of Sciences, *under review*.

Research Project 3: Project Title and Purpose

Racial Differences in Atherosclerosis and Plaque Vulnerability in Cardiovascular Disease - Cardiovascular disease (CVD) is the leading cause of death in the United States. Blacks are disproportionately affected by CVD, with a 29 percent higher age-adjusted coronary heart disease death rate and a nearly twofold higher prevalence of stroke than whites. In Pennsylvania, blacks have about a nine-year lower median age for CVD death than whites. These observations are only partially explained by racial differences in prevalences of traditional CVD risk factors. Despite having higher rates of CVD, blacks are less likely than whites to have severe obstructive arterial atherosclerosis. Accordingly, the investigators hypothesize that blacks are more likely to have vulnerable atherosclerotic plaques. This research project will investigate relationships among race, anatomic extent of atherosclerosis, measures of plaque vulnerability, and CVD events.

Anticipated Duration of Project

1/1/2008 - 12/31/2011

Project Overview

Compared to whites, blacks have higher rates of heart disease, stroke, and cardiovascular death. This disparity is only partially explained by racial differences in prevalences of traditional CVD risk factors. Nevertheless, blacks are less likely than whites to have severe obstructive coronary artery atherosclerosis. These findings are counterintuitive, in that black race is associated with anatomic findings expected to confer lower CVD risk (i.e., less arterial obstruction), despite being associated with higher prevalences of other CVD risk factors and a higher incidence of CVD events. The investigators hypothesize that compared to whites, blacks are more likely to develop vulnerable atherosclerotic plaques that are associated with acute CVD events. Preliminary investigations from the team's Heart Strategies Concentrating On Risk Evaluation (Heart SCORE) study demonstrate racial differences in arterial characteristics that are associated with plaque vulnerability. Analyses from women in the team's National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation (NHLBI WISE) study suggest that blacks have higher levels of circulating inflammatory markers, which modulate plaque vulnerability. The goal of this project is to prospectively investigate race-related differences in the anatomic extent of atherosclerosis, circulating measures of plaque vulnerability, and CVD events. The specific aims are: (1) to determine whether black race is independently associated with less obstructive carotid artery atherosclerosis; (2) to characterize race-related differences in circulating modulators of vulnerable atherosclerotic plaque; and (3) to investigate relationships among black race, carotid artery obstructive atherosclerosis, circulating levels of modulators of vulnerable plaque, and long-term CVD risk.

This project will be conducted in the Heart SCORE study cohort. Heart SCORE, which began in 2002, is an ongoing longitudinal community-based participatory research study of 2,000 participants (43 percent black) in western Pennsylvania. This project will measure obstructive carotid artery atherosclerotic plaque using ultrasonography and will assess serologic markers of plaque vulnerability like inflammatory mediators, matrix metalloproteinases, markers of

endothelial activation and dysfunction, and endothelial cell adhesion molecules. It will then prospectively tabulate CVD events during three years of additional follow-up of participants.

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Expected Research Outcomes and Benefits

Blacks have higher rates of CVD events and mortality than whites. The explanation for racial disparities in CVD is uncertain and is likely multifactorial. Investigations of biological mechanisms for CVD disparities demonstrate a paradox: compared to whites, blacks have less extensive atherosclerotic artery blockage despite having higher prevalence of CVD risk factors and a higher incidence of CVD events. Based on these observations and preliminary studies, the investigators hypothesize that blacks are more likely to develop vulnerable atherosclerotic plaques associated with acute CVD events. The goal of this project is to prospectively investigate race-related differences in atherosclerosis pathophysiology in the extensively characterized Heart SCORE cohort. The research team will assess the extent of atherosclerotic blockages in carotid arteries using ultrasonography, measure serologic factors associated with plaque instability and destabilization, and follow participants for CVD events. It is anticipated that this project will demonstrate that blacks have higher levels of modulators of plaque vulnerability for any degree of carotid artery atherosclerotic obstruction. This finding will provide mechanistic insight into racial disparities in CVD and will serve as the foundation for the development of race-specific pathophysiologic-based prevention and treatment strategies to reduce racial CVD disparities.

Summary of Research Completed

The sample size initially proposed in our strategic plan (1,125) has been reduced to 850 (with permission from PA DOH). We recently secured American Recovery and Reinvestment Act (ARRA) funds to add an additional method to assess characteristics of plaque vulnerability, allowing us to focus our CURE funds on more sophisticated hypotheses to investigate racial differences in obstructive carotid atherosclerosis. Specifically, the reduced sample size allows us to better focus our resources on expanding the measurement of cardiovascular disease markers, specifically, plasma vitamin D levels

During this reporting period, we continued to enroll participants in each of the five procedures outlined in our strategic plan. We enrolled 1,308 participants for: (1) follow-up for CVD events, current medications, and symptoms; (2) measurement of traditional risk factors (e.g., lipids); and

(3) psychosocial and socioeconomic questionnaires. We also collected plasma from 289 participants for fasting venous blood assessment of modulators of atherosclerosis and vulnerable atherosclerotic plaque, which is measured once in each participant and will be compared to carotid imaging data. The following measurements of modulators of vulnerable atherosclerotic plaque were performed:

- Soluble intercellular adhesion molecule (sICAM): 781 participants
- Endostatin: 778 participants
- Interleukin-6 (IL6): 759 participants
- CD40 ligand (CD40L): 778 participants
- Adiponectin: 769 participants
- High-sensitivity C-reactive protein (hsCRP): 751 participants

Two hundred eighty-nine participants also underwent ultrasonographic assessment of obstructive carotid atherosclerosis. Nearly 2,700 samples from the entire cohort and those who underwent ultrasonography are currently awaiting analysis of vitamin D levels. Complete data analyses will be performed after all 850 participants undergo ultrasonographic assessment of their carotid arteries, which is scheduled to be completed in summer 2011.

We have made significant progress toward our proposed milestones for this reporting period:

(1) Recruit 440 Heart SCORE participants to undergo ultrasound protocol-

Two hundred eighty-nine additional (total 804 out of a project goal of 850) participants completed the ultrasound protocol.

(2) Collect annual follow-up data on 1,400 Heart SCORE participants-

We collected annual follow-up data on 1,308 participants during this reporting period.

(3) Collect serologic samples (risk factors and atherosclerosis modulators, as indicated) on 1,400 participants-

Serologic risk factors were measured in 1,308 participants during this reporting period.

Additional samples have been collected from 289 new participants in the carotid ultrasonography section and stored for batch measurement of atherosclerosis modulators.

(4) Interim data analyses-

We have not performed interim data analyses because our sample size is not yet sufficient and analyses of serologic samples were only recently completed.

During this reporting period and based on preliminary data that were generated from this project, the investigators applied for a National Institutes of Health (NIH) R01 award, entitled “Vitamin D as a Modulator of Racial Differences in the Atherosclerotic Process.” This application is currently under review at the National Heart, Lung, and Blood Institute (NHLBI).

Research Project 4: Project Title and Purpose

Synthesis and Testing of Peptide-Guided Dual Detection Dendrimers for Cancer Imaging - This project uses a small protein fragment (peptide) known to target the blood supply of cancers to specifically deliver imaging agents to cancers. The targeting peptide is attached to the core of the imaging agent, known as a dendrimer, which, built with multiple branching units, carries gadolinium molecules that provide the magnetic resonance imaging (MRI) signaling. The core is also a dye with spectral properties that allow its detection in the near-infrared range. Thus, the

coupling of the targeting peptide to the core enables two different ways to locate tumors using a single agent. This project will establish the step-wise chemical synthesis of this targeted dual imaging agent and test it at each synthetic iteration. The project is a proof of concept of targeted imaging for dual detection of cancer, which will be performed in tumor-bearing mice with the final synthesized dendrimer.

Duration of Project

1/1/2008 - 12/31/2008

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 5: Project Title and Purpose

Molecular Mechanisms of Neovascularization - The long-term goals of this research are to elucidate molecular mechanisms of neovascularization, the development of blood vessels during physiological and pathological processes, and to explore therapeutic approaches to inhibit blood vessel growth in human breast and pancreatic cancers and malignant gliomas. In this project, the investigators will examine the signaling pathways by which vascular endothelial growth factor and inhibitor modulate neovascularization.

Duration of Project

1/1/2008 - 12/31/2008

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

Stem Cells in Esophageal Cancer - The tumor stem cell is currently hypothesized to be responsible for cancer initiation, development, metastasis, and relapse, thereby serving as a potential cellular target for cancer therapies. In this project, the investigators will study stem cells from esophageal cancer. This project will combine the powerful techniques of immunohistochemistry and flow cytometry to develop a detailed profile of normal and malignant esophageal stem cells and map them to their anatomical niches.

Duration of Project

1/1/2008 - 7/31/2009

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

Stem Cells in Prostate Cancer - The tumor stem cell is thought to be responsible for cancer initiation, development, metastasis, and relapse. Therefore, it could be a potential cellular target for cancer therapies. In this project, the investigators will identify and study the role of pericytes, which are stem cells that control angiogenesis, in prostate cancer.

Duration of Project

1/1/2008 - 12/31/2008

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

Identification of MicroRNA Regulation Targets in Breast Cancer by Quantitative Proteomics - MicroRNAs (miRNAs) are short segments of non-coding RNA that represent an important class of biomolecules that have recently been shown to deregulate the expression level of tens to hundreds of target gene products. Enzyme-miRNA complexes recognize, bind, and degrade a target message, thereby preventing protein production. More than 400 miRNAs have been identified to date, leading to speculation that the expression of every human gene might be modulated by miRNA activity. Despite growing knowledge of the catalog of miRNAs in humans, very little is known about the complete ensemble of genes that are targeted by any given miRNA. This project will develop and apply state-of-the-art high-throughput proteomics for identification of gene products whose expression is regulated by ten miRNAs that have been implicated in breast cancer.

Duration of Project

1/1/2008 - 9/30/2009

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 9: Project Title and Purpose

Human Leukocyte Antigen Defects in Cancer Stem Cells - Cancer stem cells (CSC) are a subpopulation of cells in tumors that are responsible for metastases and recurrence of disease. The resistance of CSC to chemotherapy and radiotherapy has prompted the investigators to explore the possibility of using immunotherapy for the destruction of CSC. The clinical efficacy of this strategy requires that CSC express a set of molecules required for their recognition by the host immune system. Therefore, this project will (1) analyze CSC for the expression and functional properties of this set of molecules and (2) test strategies to correct these defects, should they exist, in CSC. The resulting information will represent important preliminary data to support the design rationale for effective therapeutic strategies targeting CSC.

Duration of Project

1/1/2008 - 7/31/2009

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 10: Project Title and Purpose

Ataxia-Telangiectasia Mutated and Programmed Death Receptor 1 Genes in Melanoma - Melanoma incidence and mortality rates continue to rise at an alarming rate, and there is currently no effective treatment for patients with advanced-stage disease. Thus, it is of fundamental importance to identify and characterize the genes that govern melanoma's development and progression. This project will assess the roles of two genes: (1) ataxia-telangiectasia mutated (ATM), a gene essential in the deoxyribonucleic acid (DNA) repair pathway, which is expressed at high levels in melanoma, and (2) the programmed death receptor 1 (PD-1) gene, for which expression can impair human tumor antigen-specific CD8+ T cells in melanoma patients, thus influencing the anti-melanoma immune response.

Duration of Project

1/1/2008 - 12/31/2008

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 11: Project Title and Purpose

Optimization of Adenoviral Vector-Based Cancer Genetic Immunization Strategies - Adenovirus vector-based vaccines are often used in cancer clinical trials. To date, no standardized, reproducible laboratory tests are available that measure cellular and humoral immune responses to adenovirus. The objective of this project is to develop, evaluate, and validate a comprehensive set of laboratory assays that will be useful for serial monitoring of patients vaccinated or infected with adenoviruses. The goal is to develop a set of immune tests that can be used to specifically follow immune responses to the virus component of genetic immunotherapy vaccines in experimental clinical trials as well as be used to test for natural infection from the environment.

Duration of Project

1/1/2008 - 8/31/2009

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 12: Project Title and Purpose

Clinical Trials in Chronic Lymphocytic Leukemia - This project will evaluate a novel combination therapy for chronic lymphocytic leukemia (CLL) that attempts to reduce toxicity associated with already proven therapies. The approach will reduce levels of chemotherapeutics while increasing levels of antibody therapeutics. Results will be evaluated with regard to patient response rates as compared to the traditional treatment regimen.

Duration of Project

1/1/2008 - 12/31/2008

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 13: Project Title and Purpose

Clinical Trials in Melanoma - This project will evaluate the clinical response of melanoma patients to novel therapeutic regimens.

Duration of Project

1/1/2008 - 12/31/2008

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 14: Project Title and Purpose

Clinical Trials in Prostate Cancer - This project will establish the safety and efficacy of a new vaccine targeted against mucin-1 (MUC-1) in patients with prostate cancer.

Duration of Project

1/1/2008 - 12/31/2008

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>.