William G. "Bill" Bankhead, Jr., and David Coley Cancer Research Program

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Researcher and Institution	Title	General Audience Abstract
Grant McFadden, University of Florida	Exploiting Oncolytic Virotherapy to Selectively Target Human Hematopoietic Cancer Stem Cells	The purpose of this proposal is to develop an oncolytic ("cancer-killing") virus called myxoma virus for a new clinical procedure to specifically eliminate cancer cells from preparations of bone marrow-derived stem cells that are needed to restore the patient immune system following high dose chemotherapy. This is a new strategy to make this therapy, called autologous blood and marrow transplantation (ABMT), available for many more cancer patients, such as those with advanced leukemias and lymphomas, who are currently ineligible for ABMT because their stem cell preparations are contaminated with their own cancer cells. The project exploits the natural ability of this virus to selectively infect and eliminate a variety of human cancer cells, including leukemic stem cells, prior to transplant but spare the normal human blood stem cells needed for immune reconstitution. The selective cancer-killing potential of this particular virus for human cancer cells has now been validated in a variety of animal models of brain cancer and metastatic melanoma. Our consortium of researchers at U Florida is unique and we believe we are now the leading research group in this new area of using onolytic virus therapy to selectively remove cancer cells from human stem cell transplants needed for ABMT. This new project offers the near term potential to establish clinical trials that will allow many more leukemia and lymphoma patients to become eligible for ABMT therapy in the future.
Alan Pollack, University of Miami	Integrated Biomarker Profiling for Individualized Prostate Cancer Therapy	Men who are diagnosed with prostate cancer face difficult decisions revolving around when and how to be treated. Current methods for determining a patient's need for treatment and the aggressiveness of the treatment needed remain problematic. We propose to better define key decision points in men who have different stages of the disease by investigating biomarkers from tissue and blood. Clinical trials have been designed

		to address key questions and gain insight into the potential applications of biomarkers when considered across patient groups. To our knowledge this approach has not been used previously and the technologies we will use to obtain and analyze prostate tissue and blood cancer cells are unique. The clinical trials will involve men with distinct options who 1) have early prostate cancer are candidates for no treatment (active surveillance), 2) have intermediate to high risk localized prostate cancer and are candidates for radiotherapy, 3) have experienced a rising PSA after surgical removal of the prostate and are candidates to receive salvage radiotherapy to the surgical area, and 4) have had spread of the cancer and have become resistant to hormone and chemotherapy. The projects are highly integrated and novel because of the application of new imaging technology to better direct prostate biopsies and analyze blood products, and the plan to investigate this in patients that have different stages of prostate cancer.
Thomas Bannister, Scripps Research Institute	Inhibition of the Transport of Glutamine, Essential Amino Acids, and Lactate as a Multi-Targeted Strategy for Cancer Chemotherapy	Cancer drugs often target unique properties of tumor cells. For example, cancers tend to grow rapidly, demand a large blood supply, and spread quickly. Tumor cells need high levels of nutrients to fuel their growth. Cancer researchers have long studied the ways by which tumors meet their high energy demands but only recently have they described techniques to find drugs that work by disrupting energy input. Many nutrients enter cells using proteins called transporters. Glutamine, an important amino acid, enters cells by a transporter. Glutamine is also a fuel for other transporters, including one that delivers essential amino acids. Tumors also use transporters to rid themselves of wastes, including lactate, which they must pump out or else they become acidic. We have recently found that a substance that blocks lactate transport halts growth and even kills human lymphoma cells. A wide range of cancer types have very high levels of the transporters for glutamine, essential amino acids, and lactate. We wish to find the first drug that blocks them. We have made experimental substances that disrupt two transporters at once and found that they kill lymphoma cells. Such drugs may be broadly

		effective, having two modes of action that both target properties shared by tumor cells. Importantly, it may prove useful even against tumors resistant to all available drugs, treating as well as preventing relapse in lymphomas and breast, brain, colon, skin, lung, and prostate cancers.
Bradley Behnke, University of Florida	Is Exercise Bad for the Tumor Microenvironment?	With any increase in energetic demand (e.g., walking up stairs, gardening, exercise) blood flow and oxygen delivery are directed toward compliant tissues; analogous to electricity following the path of least resistance. Exercise is commonly prescribed to cancer patients to combat muscle weakness and fatigue, however, little is known regarding the effect of exercise on tumor blood flow and oxidative capacity. This proposal will test the global hypothesis that exercise augments tumor blood flow and oxidative capacity, and thus induces structural and functional alterations within the tumor. The 'Specific Aims' presented herein are designed to investigate mechanisms of prostate tumor blood flow at rest, and during acute and chronic exercise as well as how exercise alters tumor oxygenation and mitochondrial function. These studies will utilize an integrative approach to study how exercise affects tumors from the cell to the whole organism level. Knowledge upon the effects of exercise on tumor function and growth are extremely important considering: 1) it is likely that exercise may enhance the blood flow and density of blood vessels in tumors and, 2) exercise in combination with various tumor-targeting agents may represent a powerful therapeutic paradigm to combat tumor growth and metastasis. Therefore, the long-term goal is to utilize the research findings from this project to translational and, ultimately, therapeutic investigations within cancer patients.
Juan Del Valle, Moffitt Cancer Center & Research Institute	Chemical and Biological Studies of Marine-Derived Non-Ribosomal Peptides	Over the last 25 years, nearly 75 percent of anticancer therapeutics approved by the FDA have been derived from natural products or are considered natural product mimics. Although the pharmaceutical industry largely abandoned natural product screening with the advent of combinatorial chemistry (the synthesis of large numbers of distinct molecules), a new pipeline of marine-derived anticancer agents has renewed

		interest in natural, product-based drug discovery. Synthetic organic chemistry acts as a bridge between the discovery of new chemical entities and their development into useful therapeutics. The invention of efficient methods to access scarce compounds is vital for the optimization of potency, selectivity, and pharmacological properties of anticancer leads. The aims of this project are to synthesize and investigate the biological profiles of bisebromoamide and lucentamycin A, two marine-derived peptides (short chains of amino acids) that exhibit potent anticancer activity and feature structural subunits unprecedented in the natural product literature. We will complete the first chemical synthesis of each compound to provide material for further biological studies. Our long-term objective is to develop analogues (synthetic compounds that have high chemical similarity to natural compounds) of promising peptide natural products for use as novel anticancer agents.
Rasim Guldiken, University of South Florida	A Novel, Low Cost, Ultra-Sensitive Nanosensor for Early Detection of Ovarian Cancer	There is a tremendous need to develop a safe, simple, cost effective, reliable method to detect early stage ovarian cancer. The lack of clear symptoms and the absence of a reliable screening test for ovarian cancer results in over 70% of women being diagnosed after the disease has spread beyond the ovary so that the prognosis is poor. Patients with ovarian cancer have a short median survival time after diagnosis and their 5-year survival rate is less than 40%. Our goal, in this project, is to develop a prototype of a disposable, tiny nanosensor chip enabling early ovarian cancer detection by measuring urinary protein; Bcl-2. Advantages of our nanosensor are: 1) low cost (
Nicole Iovine, University of Florida	The Role of Smoking in Promotion of Crohn's disease, a Predisposing Condition to Colon Cancer	Smoking is implicated in many diseases other than lung cancer. For example, smokers are at a higher risk for developing and dying from colon cancer, and are more likely to develop Crohn’s disease (CD), a chronic inflammatory condition of the colon. CD alone is a risk factor for colon cancer. Therefore, smoking harms the intestines in at least 3 ways: 1) it triggers inflammation; 2) this inflammation is conducive to the development of CD and cancer; and 3) chemicals in cigarette smoke damage cells directly. However, the underlying mechanisms for these events are unclear. Mutation of the gene ATG16 is a risk factor for CD. ATG16 is essential to autophagy, a

		process that kills bacteria. When ATG16 is mutated, our cells kill bacteria less well, and resulting bacterial persistence promotes inflammation. Persons with mutant ATG16 are ~8 times more likely to have CD if they smoke, but whether their disease is more severe is unknown. We propose that smokers with mutant ATG16 will have more severe CD, and we will study this by reviewing their medical and smoking histories. Next, we propose that white blood cells (WBC) are negatively affected by smoking and ATG16. We will study this by measuring bacterial killing and inflammatory chemicals from WBC in these patients. This work is important because it will aid our understanding of how behavior and genes interact to alter our risk for CD and cancer, and will allow for improved risk-stratification and patient care.
Liyuan Ma, University of Central Florida	A High Throughput Cell-Based Metabolic Analysis of Anticancer Drugs Using Nanostructure-Enhanced Mass Spectrometry	For majority cancer patients, chemotherapy is mostly used as a systemic treatment where drugs travel throughout whole body to reach and kill fast growing cancer cells. Ideally, a drug should reach the site of action intact, kill cancer cells, and leave the body after it completes its mission. But, a potential drug can be either metabolized or excreted from the body too fast, that the drug cannot reach its therapeutic effects, causing drug resistance, or too slow, that it stays inside the body for a long time, causing side effects. Thus, the ability to detect and quantify the metabolic products of anticancer drugs is very important for anticancer drug design, preclinical and clinical pharmacology, and toxicology. But, the analysis of small drug metabolic products is challenging for most existing techniques because of the wide variety of metabolites at different abundance. This new investigator research project will develop a novel high throughput technique to analyze the cellular level metabolic products of anticancer drugs by combining nanostructure enhanced laser desorption/ionization mass spectrometry, and aptamer based on-chip separation and enrichment. This proposed new method has the potential to be more efficient than existing techniques for anticancer drug screening. Therefore, the research project fits in the long term goal of the Bankhead-Coley cancer research program.

Shunbin Ning, University of Miami	Regulation of miR-155 by oncogenic IRFs in EBV Latency and Associated Tumors	Virus infection accounts for up to 20 percent of cancers. Epstein-Barr Virus (EBV) was the first identified human cancer virus and is associated with a large range of malignancies of lymphocytic and epithelial origin. Interferon Regulatory Factors (IRFs) are a small family of transcription factors (proteins that bind to specific DNA sequences and regulate gene expression), some of which possess oncogenic properties. Interestingly, these oncogenic IRFs are associated with EBV latency, and may account for the regulation of cellular growth regulatory genes and even microRNAs (miRNAs). (MicroRNAs are a class of small non-coding regulatory RNAs that imperfectly bind to mRNA and regulate gene expression). miR-155 is an miRNA that has been implicated in many human B cell lymphomas including EBV-associated lymphomas, and like oncogenic IRFs, is associated with EBV latency. However, little is known about how miR-155 expression is regulated in cancers, and the relation between oncogenic IRFs and miR-155 in EBV latency and associated tumors has not been studied to our knowledge. The project will focus on: transcriptional regulation of miR-155 by oncogenic IRFs, the correlation between oncogenic IRFs and miR-155 in EBV latency and associated tumors, and the potential contribution of the IRFs/miR-155 interaction to EBV transformation. This research may lead to better understanding of IRFs-mediated tumorigenesis and may benefit the treatment of viral infection and prevention of cancers caused by viral infection.
Jean Wright, University of Miami	Molecular Genetics of Radiation-Induced Skin Toxicities in a Tri-Racial/Ethnic Post-Mastectomy Breast Cancer Cohort	Studies show that radiation therapy after mastectomy for breast cancer, or post-mastectomy radiation (PMRT), improves survival in high-risk patients. PMRT carries the risk of side effects, including damage to the skin, or early adverse skin reactions (EASR), including skin reddening/darkening, peeling, and pain. In patients receiving PMRT, EASR are common because the skin is part of the radiation target, and result in a treatment break in up to 1/3 of patients, which can cause increased risk of breast cancer recurrence. The severity of EASR is variable; studies suggest that genetic factors and racial and ethnic differences play a critical role, with minority populations often developing more severe side effects and requiring treatment breaks. These

		factors may contribute to the finding that minority populations have a higher risk of dying from breast cancer. We propose to develop a study examining relationships between genetic factors and EASR in patients receiving PMRT. We will collect blood samples before and after radiation for genetic analysis, assess radiation-induced EASR, and perform statistical analyses to determine associations between genetic factors and EASR. Ultimately, the proposed work could lead to identification of genes that increase the risk of EASR due to radiation. Identifying these genes could lead to changes in radiation therapy to decrease toxicity and resultant treatment breaks, ultimately increasing survival in breast cancer patients.
Barbara Curbow, University of Florida	Health Disparities in Colorectal Cancer Treatment Decision Making	Colorectal cancer accounts for 9.9% of all new cancers in the US and 10.2% of all new cancers in Florida. While early detection and appropriate treatment can improve survival, colorectal cancer is still the third deadliest cancer in the US. Unfortunately, colorectal cancer is surrounded by some significant health disparities. Not only are Blacks more likely than Whites to be diagnosed at a more advanced stage of disease, race, age, gender, and income appear to interact to influence whether patients receive all the treatment they need to survive. The reasons for these disparities are not clear but we suspect that one source of disparities is in the decision that patients make to have or not have adjuvant chemotherapy after they have initial treatment. The purpose of this study is to explore what influences some patients not to have adjuvant chemotherapy, even if it may have survival benefit for them. We will study a group of patients from before they have a colonoscopy to detect cancer all the way through their decision making to have adjuvant chemotherapy. We are particularly interested in their early interactions in the disease process with their primary care physicians and gastroenterologists. Are there any “cues” in their communications that lead patients to think adjuvant chemotherapy is a good or bad thing for them? Also, we are interested in the advice they receive from other members of their care team (nurses, surgeon) and their own caregivers.
Elizabeth Franzmann,	Early Detection Markers	Head and neck squamous cell carcinoma (HNSCC)

University of Miami	for Smoking-Induced HNSCC	is a debilitating and deadly disease that strikes 50,000 people in the United States each year and is cured only 50% of the time, largely because patients are diagnosed in late stage. African American patients and those of low socioeconomic status suffer disproportionately from this disease for reasons that are poorly understood but may have to do with exposure to risk factors such as tobacco. Prior work has identified a higher HNSCC incidence and smoking prevalence in Liberty City, a minority-rich and economically disadvantaged neighborhood within Miami-Dade County. Our laboratory is developing a simple and inexpensive early detection test designed to alleviate the burden of this disease in high-risk populations like Liberty City. In Aim 1 we will determine the levels of solCD44 and protein in oral rinses from subjects enrolled in a Liberty City head and neck screening clinic and examine a) how they vary with demographic and risk factors and b) how they change over time. In Aim 2 we will determine changes in oral rinse solCD44 and protein marker status with smoking cessation and in Aim 3 we will evaluate perceived acceptability of the test and its likelihood to influence smoking cessation in the population. This work will help determine whether this simple and inexpensive oral rinse test is likely to relieve the burden of HNSCC in high-risk communities such as Liberty City.
Maria Zajac-Kaye, University of Florida	Design, Synthesis and Evaluation of Novel Selective Inhibitors of FAK and IGF-1R Function in Pancreatic Cancer	Pancreatic cancer (PC) is a leading cause of cancer death in the U.S and there is no effective therapy. Human cancer cells grow and survive due to the overabundance of focal adhesion kinase (FAK) and insulin-like growth factor receptor-1 (IGF-1R). FAK interacts with IGF-1R, which contributes to the malignant behavior of PC. Our data shows that inhibition of both FAK and IGF-1R increases PC death compared to inhibition of either protein alone. Scientists are evaluating many drugs that inhibit the enzyme function of FAK or IGF-1R. However, these drugs are not very specific or effective resulting in increased side effects and little ability to prevent PC growth. Recently, the approach of inhibiting direct protein interactions rather than enzyme function has been shown to be effective. Our hypothesis is that the protein interaction of FAK with IGF-1R is favorable for PC and promotes PC growth and survival. Our studies

		will identify novel compounds that will prevent the protein interaction of FAK and IGF-1R. These compounds will have widespread effects by inhibiting the cellular processes that FAK and IGF-1R control including cell growth and survival. In addition, this effect will be specific for FAK and IGF-1R with minimal inhibition of other molecules, therefore, decreasing potential side effects of these compounds. Targeting FAK and IGF-1R protein interactions in PC will allow for the development of more specific and effective treatments for patients with this deadly disease.
Jennifer Hu, University of Miami	Impact of Molecular Genetics on Disparities of Breast Cancer Risk and Prevention	Breast cancer is a serious public health challenge. Minorities, low income, and medically underserved women remain at a higher risk of dying from breast cancer. Therefore, the elimination of the unequal burden of breast cancer is one of our overarching long-term research goals. To achieve our long-term goals in reducing breast cancer disparities, the proposed research will evaluate breast cancer risk prediction models and to identify targets for intervention. We hypothesize that breast cancer with worse diagnosis occur more frequently in underserved minorities due to: (1) genetic defects in DNA repair, (2) elevated DNA damage, and (3) gene-environment interactions. We will test a new paradigm that genetic and non-genetic regulation of DNA damage/repair contributes to breast cancer disparities. Investigating this new paradigm will identify women at high risk of more aggressive cancer who will benefit from targeted interventions. With a well-established study design, exciting preliminary data, lab expertise, and a large underserved minority patient cohort (n=3,200; 40% minorities), this will be the largest and most comprehensive evaluation of molecular genomics of DNA damage/repair of minority breast cancer patients to date. The results will impact breast cancer risk assessment, treatment, intervention, and ultimately improve survival of underserved and understudied minority breast cancer patients with more aggressive tumor phenotype and worse clinical outcome.
Krishna Komanduri, University of Miami	Improving Cord Blood Transplantation Via Expansion of Myeloid and Regulatory T Cells	Allogeneic stem cell transplantation (SCT) is the primary curative therapeutic modality for many patients with relapsed and/or high-risk hematologic malignancies. Unfortunately, many

		patients who might otherwise be cured by SCT are unable to be transplanted due to the lack of a suitable family or registry donor. For these patients, historically discarded placental and umbilical cord blood (CB) represents a potentially life-saving source of hematopoietic cells. Unfortunately, cord blood transplantation (CBT) is limited by delayed recovery of donor-derived cells, including those that fight infection. This is particularly true in adults, because the numbers of cells in CB products are often too few to promote rapid recovery of recipient white blood cells and immune function. Poor immune recovery often leads to infection, which is the major cause of death after CBT. In the studies of this proposal, we plan to conduct two trials where CB products are manipulated outside of the body to significantly expand cell numbers. The first will use a novel expansion strategy to try and improve white blood cell recovery and function in recipients. The second trial will additionally expand a special white blood cell population capable of preventing graft-versus-host disease, an important complication of CBT. In both studies, we will carefully assess recipient clinical outcomes and, using novel methods, the impact of our interventions on recipient immune recovery.
David Lee, University of Miami	Florida Cancer Health Disparities: the FCDS/NCHS Cancer Linkage	Since 1986, over 1.8 million adults have participated in nationally representative health surveys of the National Center for Health for Health Statistics (NCHS) including the National Health Interview Survey (NHIS). Collectively, these surveys contain substantial information on demographics, medical expenditures, health status, health behaviors, including cancer specific and risk factors; in addition, there are periodic cancer supplements (e.g., screening behaviors), as well as mortality linkage. Our LONG-TERM objective is to seek R01 funding to create a Consortium to perform a data linkage with the 1.8 million records from these studies with all State cancer registries (including SEER). Using Florida Cancer Data System (FCDS) records, representing ~6% of total US annual cancer incidence, we will establish the feasibility of developing such a Consortium by: 1) Comparing cancer-related Florida NHIS data (e.g., cancer screening, smoking behaviors) with data from the other 49 states to

		explore health disparities; 2) Performing a FCDS cancer registry linkage with NHIS data and depositing a de-identified file at the NCHS Research Data Center for merging with linked NHIS files; 3) Analyzing linked FCDS-NHIS data to demonstrate its utility to perform hypothesis-driven research in health disparities, cancer control and prevention; and 4) beginning recruitment all US cancer registries into the Consortium in the preparation of an National Cancer Institute R01 application.
Hendrik Luesch, University of Florida	Chemistry and Biology of Apratoxins	Natural products show outstanding potential as starting points in drug discovery, especially in the quest for anticancer drugs. Over half of the currently approved anticancer drugs are derived from natural products but are directed against a small number of targets in the cancer cell. The objectives of the proposed research are the validation of a new mechanism of drug action for anticancer therapy and the assessment of the therapeutic potential of a class of marine natural products termed apratoxins which act via this unexplored mechanism. Our preliminary data indicate that apratoxins deplete cancer cells of several certain receptors and other proteins that are overexpressed or overactive in cancers. Apratoxins interfere with the synthesis of these cancer-associated molecules, and we test the possibility that inhibition of their synthesis may be exploited for anticancer drug development. The research proposed here will characterize the mode of action, structure-activity relationship and anticancer drug potential of the apratoxins and, more generally, this mechanism, and identify targets for rational combination therapy.
Seigo Nishida, University of Miami	A Novel Immunotherapy for Liver Transplant Patients with Hepatocellular Carcinoma: Anti-Tumor Effect of IL2-activated Donor Liver Natural Killer Cell	Liver cancer is the third leading cause of cancer related deaths in the world, and frequently occurs in patients with liver cirrhosis from viral hepatitis. Liver transplantation is one of the best treatment options for patients with liver cirrhosis and liver cancer and is frequently performed in the United States. However, liver tumors return in about 10-20 % of these patients even though chemotherapy is performed, highlighting the need for additional therapies. More than 30 years ago, blood cells were found which can kill cancer cells. These cells were named natural killer (NK) cells. The mechanism of killing and the character of NK cells

		are now better known. Recent advancement of research has made it possible to purify, educate, and activate NK cells. Our laboratory has been able to take out cells from the donor and activate them to kill cancer cells without harming the patient. We plan to use this method in liver transplant patients with liver cancer. We intend to study NK cells and clarify its mechanism of killing the cancer cells. Although NK immunotherapy has been tried, this method has never been applied to liver transplantation with liver cancer. The goal of our program is to improve the quality of life of the patient through advancement of scientific research.
Tuya Pal, Moffitt Cancer Center & Research Institute	Inherited Cancer Registry (I CARE) Initiative	The discovery of the BRCA genes almost 15 years ago, allows us to identify people who have changes in these genes. A woman with a gene change has a high chance to develop breast and ovarian cancer. Yet, it is still difficult to spot people with these changes due to the small number of medical experts familiar with the BRCA genes. As such, many practitioners and patients in the community are not aware of these genes. Roughly 5% of all people with BRCA gene change know that they carry this change. In Florida, we have the second highest number of new cancer cases and very few experts in the topic of Clinical Cancer Genetics. Because of this, many practitioners and patients are less aware about the topic of BRCA mutations, which could possibly lead to misinformed healthcare decisions. We propose to boost access of information about BRCA gene changes to healthcare providers and patients, through using an existing network of community practitioners (called the 'Moffitt Affiliate Network' (MAN). This would allow MAN practitioners to reach to Moffitt-based experts for information on subjects related to how to identify and manage those with BRCA changes. Patients with BRCA changes from MAN sites would also be able to join our Inherited Cancer Registry (ICARE). This registry would carry out research on those with BRCA gene changes to develop better care options for them. The eventual goal of our efforts is to improve the care given to those with BRCA gene changes in Florida.
Tuya Pal, Moffitt Cancer Center	Black Women: Etiology and Survival of Triple-	Young Black women get breast cancer less often than White women, but are more likely to die from

& Research Institute	negative Breast Cancers (BEST) Study	it. This may be caused by a type of aggressive breast cancer called 'triple negative' (TN) disease, which is more common in Black women. We plan to study why young Black women get the more serious type of TN breast cancers. We will recruit 600 Black women diagnosed with breast cancer at or below age 50, through the Florida State Cancer Registry. Based on our earlier study in similar women, we believe we can accomplish our goals. We will collect information about each of the 600 participants through a detailed questionnaire, medical records review, and genetic testing. The participants will also be followed every 2 years for the duration of the study to track how they do. Our study would provide no cost genetic counseling and testing for the participants in this study. The test results could allow the study participants and their families to make important decisions about their healthcare. The researchers working on this study include Black community members. They help us make sure our research is relevant, the recruitment and study procedures are conducted in a sensitive manner, and help share important study findings with the Black community. Through our study, we hope to better understand why young Black women get TN breast cancers and why they die from the disease more often. Ultimately, we need this information to lower the number of TN breast cancers in these women.
Peter Storz, Mayo Clinic	Protein Kinase D - A Marker and Target for Invasive Breast Cancer	A difficulty in breast cancer therapy is that clinically-used compounds that mainly target proliferating cells are not very effective in targeting invading cells to prevent recurrence. There is a need to identify key-proteins modulating tumor cell invasion, which can serve as new drug targets. Another issue is that molecular markers are lacking which allow predicting metastatic breast cancer or recurrence. In this proposal we will investigate if a protein named PKD1 is a molecular switch that acts as a suppressor of breast tumor cell invasion. We will test if this can be utilized to predict the potential for metastasis or recurrence of tumors and to develop new avenues for therapeutic intervention. Our goals are to understand the mechanisms by which PKD1 is inactivated in highly-invasive breast cancer cells and if this inactivation can serve as a

		predictive marker for the potential of tumors to metastasize (goal 1); to understand the mechanism this protein utilizes to mediate its anti-invasive functions (goal 2); and to test a reactivation strategy for PKD1 as a therapeutic approach (goal 3). Successful completion of this proposal will identify new prognostic markers for metastatic breast cancer and tumor recurrence. A second outcome is that we will re-activate a silenced tumor suppressor, which is a novel and innovative strategy and once tested in our orthotopic animal model will allow a relatively quick adaption for a clinical application in phase I trials.
E. Aubrey Thompson, Mayo Clinic	Translational Genomics of Triple Negative Breast Cancer	Triple negative breast cancer affects some 30,000 women yearly in the U.S., with a predominant effect on young women and those of African descent, and is the most challenging type of breast cancer from a clinical standpoint. The disease is heterogeneous, some women do well while others do poorly; and there are no targeted therapies available for this type of breast cancer. Thus, there are two pressing clinical needs. We need new biomarkers to assess the risk of relapse in women with triple negative cancer, and we need to identify new therapeutic targets for treatment. These are our objectives. We will use massively parallel DNA sequencing protocols to identify a novel sort of mutation that arises due to gene fusion in primary tumors from triple negative patients. These mutations are absolutely tumor specific, not found in normal cells, and are therefore ideal biomarkers for risk prediction and stratification of this class of breast cancer. Since these mutations are tumor specific, they are also ideal therapeutic targets; and our objectives include identification of fusion gene mutations (which occur when two different genes are accidentally broken and stitched back together to form a new gene) that are required for tumor survival, growth, and/or spread. Our long-term goal is to apply this technology to individual patients, identify every mutation in each tumor, and tailor therapy to the specific types of mutations that drive the tumor.
Nancy Nabilsi, University of Florida	Epigenomic Mapping of Mammary Epithelial Stem Cells and Tumor-	Despite a promising initial response to modern breast cancer therapies, many patients relapse and develop recurrent tumors. One explanation for

	Initiating Cells	disease recurrence is the existence of small populations of tumor cells that resemble stem cells. These cells are unique in their ability to continually grow, initiate tumors and evade conventional therapies. Our broad objective is to identify the unique biological properties of tumor-initiating cells. This could help us design therapies to specifically target these cells, thereby eradicating primary tumors while preventing recurrent disease. Improper genetic and epigenetic information contribute to tumor formation and disease progression. While genetic mistakes are permanent, epigenetic mistakes can be reversed, making them attractive targets for cancer therapy. Our specific aims are to isolate and characterize tumor-initiating cells from patient breast tumors and to simultaneously examine their epigenetic marks at thousands of regions across the genome. By comparing their features to those from non-tumorigenic cells we expect to identify the epigenetic abnormalities that make tumor-initiating cells unique. These findings will help us: 1) understand the origin and disease forming capabilities of tumor initiating cells, 2) uncover new targets for epigenetic based drug therapies and 3) uncover epigenetic patterns that will provide important information to cancer clinicians for diagnostic or prognostic purposes.
Lei Zhou, University of Florida	A Novel in vivo Assay System for Screening Epigenetic Modulators that De-Repress Tumor Suppressor Genes	This project aims at developing the technology transfer feasibility of a novel assay system. This proprietary system can be used for the identification of chemical compounds with cancer therapeutic values, specifically those compounds that modulate the epigenetic status or change in function of tumor-suppressor genes through targeted histone modifications. Epigenetics is control of changes in gene function that do not involve changes in DNA sequences. Epigenetic regulation plays an essential role in controlling important cellular properties such as cell survival, proliferation, and differentiation. Dysregulation of epigenetic status, such as silencing of tumor-suppressor genes, is a major underlying cause of cancer and has a direct relationship to cancer prognosis. The proposed assay system, successfully developed, will provide a novel way of screening for compounds that can modify the epigenetic status for tumor-suppressor genes. It is

		envisioned that this grant will help to improve the feasibility of the novel assay system for large-scale commercial applications.
Johnathan Lancaster, Moffitt Cancer Center & Research Institute	From BAD to Good: Developing an Assay to Predict Ovarian-Cancer-Chemo-Resistance and Survival	The development of resistance to chemotherapy contributes enormously to cancer morbidity and mortality in Florida and globally. Patients with ovarian cancer, the most lethal gynecologic malignancy, succumb to their disease when chemo-resistance develops. We recently discovered a signaling pathway (BCL2 Antagonist of Cell Death, or "BAD") that causes ovarian cancer cells to become resistant to chemotherapy and shortens survival. Findings from over 1,200 patients/cancer samples (including ovarian, breast, colon, and brain) suggest that the BAD pathway can: i) be used as a clinical test to predict chemo-resistance and short-term survival for patients with ovarian cancer and ii) be inhibited by "smart drugs" that target and inhibit the pathway to reverse chemo-resistance and prolong survival. To strengthen the economic feasibility and commercial prospects of our discovery we aim to translate our findings into a BAD pathway gene expression signature (BPGES) clinical assay, leveraging real-time polymerase chain reaction (RT-PCR)-based technology and expertise that is widely available in clinical laboratories worldwide. A BPGES assay has huge clinical and commercial potential, helping doctors guide therapy via strategies tailored to the biology of each tumor for thousands of patients each year. Funding from the Bankhead Coley TTF Grant would enable us to translate our findings to a clinical test that has potential to be commercially viable and reduce the burden of cancer mortality.
Peter Sayeski, University of Florida	Improving the Metabolic Stability of the Jak2 inhibitor, G6	Mutations in the Jak2 allele (one member of a pair or series of genes) result in a variety of disorders including various leukemias, lymphomas, myelomas, and the myeloproliferative neoplasms. In these diseases, cells rapidly divide and become resistant to the properties that govern normal cell growth. The current lack of effective treatments to inhibit Jak2 has greatly hampered our understanding of these diseases and left little hope for patients suffering from these disorders. Using high throughput computational analysis, we screened a drug database in order to identify novel Jak2 inhibitors. One compound in particular,

		herein designated as G6, was found to be a potent Jak2 inhibitor. Furthermore, it exhibits significant therapeutic effectiveness in three mouse models of Jak2-V617F mediated disease. G6 possesses a number of desirable drug-like characteristics including good aqueous solubility, high membrane permeability, high stability in plasma, and a lack of non-specific cytotoxicity. However, it is extensively metabolized by liver microsomes in vitro (a test done in glass or plastic vessels in the lab). Therefore, the purpose of this study is to identify derivatives of G6 that maintain Jak2 effectiveness, but have improved metabolic stability. As such, completion of these studies will greatly increase the commercial appeal of G6 and hence, potentially provide a new treatment for patients suffering from Jak2-mediated disorders.
Radka Stoyanova, University of Miami	Metabolic Tumor Volumes in Radiation Treatment of Brain Tumors	Proton Magnetic Resonance Spectroscopy (MRS) can be used as a non-invasive tool for accurate delineation of tumor and healthy tissue in Radiation Therapy (RT) of patients with brain cancer. Currently, Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) are used to determine the treatment volumes for radiation dose distribution. Often MRI and CT are ambiguous with regard to tumor volume and tissue viability, while MRS can provide the exact position and extent of tumor infiltration; define the tumor margin and potentially identify the areas of microscopic disease. The University of Miami (UM) has a unique infrastructure for brain imaging – a high magnetic field MRI instrument and sophisticated acquisition and analysis methods which allow for detailed volumetric metabolite data over the entire brain. In this grant we propose to utilize these invaluable resources and apply MRS for brain tumor patient management. The goal is to provide the radiation oncologists with detailed maps of tumor-involved areas. The aberrant distribution of the metabolites will be detected in comparison with a database of information from healthy controls. UM is in the unique position to evaluate the role of MRS in reshaping treatment areas. A potential outcome of the proposed study will be a more precise radiation dose delivery to the malignant tissue, thus improving treatment efficacy. In addition, by minimizing the involvement of normal brain, the

		treatment will also reduce morbidity.
Sarah McLaughlin, Mayo Clinic	Enhancing the Ability to Predict Lymphedema Development Following Axillary Surgery for Breast Cancer and its Effects on Patient Survivorship	Issues affecting breast cancer survivorship are of increasing importance as the number of women living years after breast cancer treatment grows. Following surgery for breast cancer, women worry about their risk of developing lymphedema (LE), an unpredictable, chronic arm swelling that can have a significant and debilitating impact on their lives. Indeed, many women experience considerable anxiety due to our current inability to accurately predict or modify their risk of LE. This anxiety negatively impacts their health and overall quality of life (QOL). Thus, our aims in this proposal are to (1) identify baseline tissue characteristics potentially predisposing women to LE, (2) identify markers and genetic risk factors that might be altered to prevent LE, and (3) prospectively document the time course to LE development and associated changes in QOL. This prospectively designed study includes analysis of collected biospecimens and QOL metrics at baseline and over 5 years follow up. The long term goal rests on the development of predictive tools that can help accurately predict LE, guide postoperative surveillance protocols, and more accurately pinpoint high-risk patients who might benefit from aggressive risk reduction strategies. Clinical application of these findings will help to improve research and treatment of LE after breast cancer through better risk stratification of patients for future clinical trial development related to the prevention and treatment of LE.
Olveen Carrasquillo University of Miami	South Florida Center for the Elimination of Colorectal Cancer Health Disparities (SUCCESS-CRC)	Our research team has previously shown that Hispanics and Haitians in Florida suffer a disproportionate burden of colorectal cancer. Therefore, and based on feedback from our community advisory groups, we propose to extend the work of our cancer health disparities center to now also address colorectal cancer among Hispanics and Haitians in Florida. In this Team Science Project, we will tackle this major public health problem through a series of three highly innovative studies. Our first project will develop better population based methods to track and describe the epidemiology of colorectal cancer among minority communities. This data is critical if we are to develop targeted preventive interventions. Second we propose to begin to test

		the feasibility and acceptability of more novel methods of colorectal cancer screening in some of the most vulnerable Hispanic and Haitian communities in Florida. Last, beyond screening, unique insights are also needed into the tumor biology of colorectal cancer among these vulnerable groups. This would allow for more personalized interventions. Our grant also includes a centralized core that will provide scientific oversight, research support and a mechanism for community input for all three projects. This TSP will also be critical in helping us secure additional federal support to continue our ongoing work in cancer health disparities.
Aysegul Gunduz, University of Florida	Derivation of Molecular Signatures for Accurate Breast Cancer Prognosis	Previous studies have demonstrated the potential values of molecular signatures in assessing the risk of post-surgical breast cancer recurrence. However, many existing prognostic models were developed based on a limited number of samples, and their optimality has not yet been well established. Due to a high incident rate of breast cancer, a large number of tumor tissues have been archived, the majority of which lack clinical follow-up information. The goal of this project is to investigate whether we can use data obtained from these non-annotated samples to significantly improve prognostic accuracy by using advanced computational techniques, and thus pave the way for future multi-institutional cohort studies. To this end, a new computational algorithm will be developed to efficiently mine information from both annotated and non-annotated data, and advanced machine learning algorithms will be used to derive accurate prognostic signatures. A large-scale validation study will be performed to evaluate the performance of the constructed prognostic model against existing approaches on publicly released datasets. If successfully implemented, this work will have a significant impact on cancer research and patient management, and lead to a paradigm shift in the derivation and validation of gene signatures for accurate breast cancer prognosis. The developed innovative approach can also be used in other cancer studies where the lack of follow-up information is a ubiquitous problem.
Kevin Brown, University of Florida	Epigenetic Basis of Neoplastic Progression	Cancer arises and progresses due to alterations within DNA stemming from both changes in DNA

	in Human Cancers	sequence (genetic alterations) and DNA structure (epigenetic alterations). This Bankhead-Coley Team Science Project, an inter-institutional effort between investigators at the University of Florida and the Moffitt Cancer Center, is focused on understanding how epigenetic alterations impact the process of colorectal and cervical cancer progression and if these alterations can be used as markers to predict disease behavior. Project 1 focuses on discovering epigenetic events useful in the identification of women at risk of developing more aggressive forms of cervical cancer. This will be done using state-of-the-art molecular methodologies to measure DNA methylation at various stages of cervical cancer progression coupled with rigorous epidemiological analyses. Project 2 is focused on using an innovative technology developed by our group that examines DNA structure at the molecular level and will be used to study changes in DNA structure during colorectal tumor progression. Project 3 focuses on CTCF, a known epigenetic modulator, and how this molecule controls blood vessel development during colorectal cancer progression. This set of overlapping research projects will provide us with needed knowledge on how epigenetics impacts cancer progression, and has strong potential to discover molecular events that can be used clinically to predict tumor behavior at early disease stages.
Lori Hazlehurst, Moffitt Cancer Center & Research Institute	Targeting the Tumor Microenvironment in Multiple Myeloma	Multiple myeloma (MM) often responds well to standard therapy initially. However, drug resistance inevitably emerges, and all patients eventually die of recurrent disease that is resistant to available treatments. Therefore, identification and validation of novel therapeutic strategies and understanding the evolutionary dynamics of resistance are essential for improving the clinical outcome of patients with MM. In this grant, our group, composed of investigators with expertise in biology of myeloma, mathematical modeling, clinical investigations, pharmacology, and chemistry, will use diverse hypothesis-driven strategies to target MM cells residing in the bone marrow. Our grant consists of 5 projects: Project 1 will focus on pre-clinical development of c-HYD1, a cyclized peptide targeting VLA-4-CD44 containing complexes; Project 2 will test novel CRM1

		inhibitors for increasing the efficacy of topoisomerase II inhibitors; Project 3 is based on an interesting observation that Notch inhibitors are devoid of activity in vitro yet have significant anti-MM activity using in vivo models; Project 4 will examine the role of the FA pathway in mediating de novo and acquired resistance using a co-culture model system; and Project 5 will develop evolutionary based models for testing strategies for combining therapeutic agents for maintenance of minimal residual disease.
Jin Cheng, Moffitt Cancer Center & Research Institute	microRNA-155 in Breast Cancer	Previous studies have shown that microRNA (miR)155 is one of the most frequently elevated miRNAs in breast cancer. However, its role and importance in this malignancy are currently unknown. We have recently shown that elevated levels of miR-155 are closely associated with invasive breast cancer, recurrence and poor prognosis as well as chemoresistance. Overexpression of miR-155 in breast cells induces epithelial-mesenchymal transition (EMT), cell migration and invasion. Further, miR-155 is elevated in breast cancer stem cells (BCSC) and enforced expression of miR-155 induces BCSC growth. These findings suggest that miR-155 plays a pivotal role in breast cancer metastasis, chemoresistance and development, and thus miR-155 is a critical therapeutic target for breast cancer intervention. In this proposal, we will first determine the role of miR-155 in breast cancer development and metastasis in a mouse model. Finally, we will ascertain the causal factors for alteration of miR-155 in breast cancer, which could lead to identifying the new therapeutic targets for breast cancer intervention. These investigations will uncover miR-155 as a key causal factor for breast cancer development and metastasis as well as a critical therapeutic target for treatment of this malignancy.
David Gilbert, Florida State University	Replication Profiling as a Diagnostic Tool in B-cell Acute Lymphoblastic Leukemia	We propose to explore a novel source of cancer biomarkers—the temporal order in which segments of chromosome are replicated (“replication timing”)—that has great potential impact in identifying good and poor risk patients and further personalizing therapeutic approaches to cancer. Abnormal replication timing has been anecdotally associated with many cancers, but no systematic evaluation of its potential to serve as a

		source of biomarkers has been performed. We will focus on B-cell Acute Lymphocytic Leukemia (ALL) as a model cancer. Not only is ALL the most common form of childhood cancer, but the characterization of several genetic subtypes and the availability of relatively homogeneous cancer tissue from patients make ALL a good model in which to explore novel biomarkers. Our hypothesis is that replication timing will be different in different subtypes of ALL and that these differences can be exploited for therapy as well as to improve clinical outcome. We have developed a rapid and simple way to measure replication timing and have identified unique patterns in a handful of patient samples. Our proposed objective is to acquire sufficient samples to demonstrate feasibility and construct an analytical plan that will warrant a federally funded study to link these markers to patient outcome. This is a unique approach that may open the door to an entirely novel avenue in the development of cancer biomarkers.
Huabei Jiang, University of Florida	Combined Photoacoustic and Diffuse Optical Tomography	Breast cancer remains a major public health problem in Florida and the United States. There are ~200,000 new cases of breast cancer diagnosed in the United States, making it the most common cancer affecting women. Early detection and diagnosis of breast cancer is very important as early stage breast cancer is much easier to treat and more easily cured than breast cancer diagnosed at more advanced stages. Currently available imaging modalities (mammography and ultrasound) are very limited in their ability to detect and diagnose early breast cancer. New, effective approaches to early detection and diagnosis of human breast cancer are desperately needed. In this interdisciplinary proposal, we seek to engineer a novel human breast imaging system that uses safe near infrared light and sound waves (Combined Photoacoustic and Diffuse Optical Tomography) to diagnose breast cancer. Hardware and software development will be the early focus of the project. The novel combined imaging system will then be tested in human breast phantoms to optimize performance. Finally, for the first time, the combined imaging system will be used to evaluate breast masses in human subjects. It is anticipated that data obtained from

		this work will form the basis of a future successful federal grant application that will allow continued development of this novel combinatorial imaging modality towards clinical application for ultimately reducing suffering and improving survival related to human breast cancer.
Michael Wallace, Mayo Clinic	Confocal Endomicroscopy for Colorectal Neoplasia	Screening for colorectal cancer with colonoscopy is effective, safe, and widely used in the United States. Colonoscopy can detect small growths called 'polyps' but many of these will never become cancer; however, the only way to currently determine this is to remove the polyp and perform examination through standard microscope, a procedure which increases the risk and cost of colonoscopy. In this study, we will determine whether a novel fiber-optic miniature microscope can accurately detect and classify pre-cancerous growths inside the colon, and thus limit biopsy only to those growths that are pre-cancerous.
Paolo Serafini, University of Miami	A nanobased immunediagnostic approach for monitoring the immune response in HNSCC	A new era for the treatment of cancer started with the first therapeutic anti-cancer vaccine approved by the FDA in 2010. An increasing number of options for the treatment of tumors are being developed with the idea to instruct our own immune system to fight and kill the cancer cells. Despite the enthusiasm that these new approaches have generated, it is becoming clear that, in order to succeed, different immune therapeutic treatments will need to be combined. The identification of the most promising therapy is thus a necessity and requires the generation of new, cost effective, and easy to perform methods to monitor the capacity of the immune system to be able to recognize and kill cancer cells. In fact, today's methods are expensive and either poorly reliable or require specialized laboratories. By taking advantage of the technology advancement in the science of nanomaterial, we develop a new product that allows monitoring the tumor specific immune response. Preliminary data and cost analysis seems to indicate that this kit is more sensitive and much more cost effective of the currently used techniques and, more importantly, it does not require specialized laboratories with highly trained technicians. With this proposal we will evaluate the efficacy of this method in Head and Neck Cancer, and we will compare the data

		obtained with the one generated using the most reliable (but extremely expensive and complicated to perform) method to measure the anti-cancer immune response.
Yanxia Liu, University of Florida	Development of scale-up synthetic method for Largazole, a novel drug for the treatment of colorectal cancer	Natural products show outstanding potential as starting points in drug discovery, especially in the quest for anticancer drugs. Our research group recently discovered a new marine natural product, largazole, with anticancer properties. The compound shows potent and selective activity against cultured cancer cells and promising activity against colorectal cancer in an animal model. Largazole inhibits an enzyme called histone deacetylase (HDAC) which is overactive in certain cancers. Selective HDAC inhibitors could be promising anticancer agents; two HDAC inhibitors have been approved over the past few years for the treatment of cutaneous T-cell lymphoma. The objective is to partner with Oceanyx Pharmaceuticals, Inc. to move largazole from bench to bedside. The first step towards that ultimate goal is to demonstrate the feasibility of large-scale chemical synthesis and to generate enough largazole for extensive preclinical testing.
Lori Hazlehurst, Moffitt Cancer Center & Research Institute	Targeting CD44 with HM-27 in AML	Acute myeloid leukemia (AML) is a disease that often initially responds to chemotherapy treatment with agents such as topoisomerase II inhibitors and cytarabine (AraC). Although these antineoplastics yield a complete remission rate ranging from 60-80%, only 25% of patients survive beyond five years. Furthermore, disease relapse is associated with a multi-drug resistant phenotype that contributes to decreased chemotherapy sensitivity and failure of salvage treatment. In AML minimal residual disease (MRD) is typically found in the bone marrow niche. We have recently discovered that our novel cyclic peptide (HM-27), which is based on the active core region of the linear HYD1 peptide preferentially, kills leukemic progenitor CD34 positive cells compared to normal CD34 positive cells. Importantly, HM-27 is more active in CD34 positive cells isolated from specimens obtained from relapsed patients compared to specimens obtained from newly diagnosed patients. Our drug candidate targets CD44 an adhesion molecule important for homing to the bone marrow and survival. The goal of this proposal will be to test rationally designed

		combination strategies in vitro and to test our drug candidate using in vivo human xenograft models.
David Reisman, University of Florida	Validate BRM polymorphism as a Biomarker for lung cancer risk	Our success in treating cancers has been hampered because many cancers are not detected until the cancer is very advanced and thus incurable. Early-stage lung cancer can be cured with surgery, and CT scanning is an effective radiological method to detect cancers early. But CT scanning is an expensive, so determining who will benefit from such monitoring remains a challenge. While smoking is the primary risk factor for lung cancer, only 10 percent of smokers develop lung cancer; thus, screening all smokers is cost-prohibitive. Further, many people who do not smoke develop lung cancer. The purpose of this research is to develop a test that could predict which patients are at greatest genetic risk for developing lung cancer and would thus benefit from CT scans and from lifestyle modifications. We have found that an anticancer gene called Brahma (BRM) frequently stops functioning in those who develop lung cancer . This gene has alterations called polymorphisms that appear to be correlated with lung cancer risk. We will analyze blood samples, health history, and other information from healthy volunteers and from lung cancer patients to see if there is a difference in whether the BRM gene polymorphism is present. This work will determine whether it is feasible to develop BRM as a new biomarker test to predict lung cancer risk, a test that could make it practical and cost-effective to use CT scans and other methods to follow those at high risk for developing tobacco-related cancers.
William A. Dunn, Jr., University of Florida	Inhibiting a core autophagy protein to treat prostate cancer	Prostate cancer is the second leading cause of cancer-related death in men. Androgen-dependent prostate cancer is most common and treatable. However, this cancer can recur as an aggressive and lethal castration-resistance form. Therefore, there is a need for an effective systemic therapy to not only promote prostate tumor regression and inhibit recurrence but also to better treat the chemoresistant and the metastatic nature of castration-resistant prostate cancer. Autophagy is an excellent target to treat cancer because of its positive impact on tumor cell survival and chemoresistance. However, drugs that can effectively and specifically inhibit autophagy in

		vivo are not yet available. We have identified and characterized a nontoxic “first-in-class” anti-autophagy compound that effectively suppresses autophagy in vivo by inhibiting a core autophagy protein called Atg4B. Furthermore, we have shown that this compound suppresses the tumor growth and promotes tumor regression of osteosarcoma xenografts. Our goal is to test the efficacy of a first generation Atg4B antagonist to inhibit autophagy induced by nutrient deprivation and chemotherapy agents in vitro and to suppress the tumor growth of androgen-dependent and castration-resistant prostate cancers in vivo. These innovative pre-clinical studies will establish Atg4B as a therapeutic target to inhibit autophagy and substantiate the use of Atg4B antagonists to treat prostate cancer.
Edward Seto, Moffitt Cancer Center & Research Institute	Functions, Mechanisms of Action, and Regulations of SIRT1	The human SIRT1 protein plays a key role in aging and cancer development. SIRT1 has been shown to have oncogenic properties but paradoxically can act as a tumor suppressor. SIRT1 functions are frequently altered in cancer cells, and a decrease in histone acetylation mediated by SIRT1 is a common hallmark of human tumors. The long-term objective of this project is to address how SIRT1 affects aging and contributes to the development and progression of cancer. Completion of these studies will add to the knowledge of cancer diagnosis and the understanding of tumor development, progression, and treatment. Together, this project will help advance the cure of cancer by utilizing laboratory-based science.
Jianfeng Cai, University of South Florida	Design, synthesis, and evaluation of gamma-AApeptide-based protein tyrosine phosphatase inhibitors as novel anticancer agents	Abnormal tyrosine phosphorylation is a frequent cause of human cancer and oncogene addiction required for the malignant state. Accumulating evidence suggest that some of protein tyrosine phosphatases (PTPs) are novel targets for developing anticancer drugs. The long-term objective of this project is to develop novel gamma-AApeptide-based compounds as inhibitors of specific PTPs that are targets for anticancer therapy. Building upon this initial success, the goal of the proposed research is to further develop gamma-AApeptide based PTP inhibitors focusing on Shp2 as the primary target. To achieve the goal, we have the following specific aims: 1. Design and synthesize novel gamma-AApeptides bearing

		phosphonate functionalities as potential PTP inhibitors. 2. Design and synthesize novel gamma-AApeptides bearing sulfonate functionalities as potential PTP inhibitors. 3. Determine the potency and selectivity of gamma-AApeptides for inhibition of protein tyrosine phosphatases in vitro and test potent and selective Shp2 inhibitors in cellular assays. The proposed project will lead to a new class of Shp2 inhibitors as novel anti-cancer therapeutics for caner prevention, diagnosis, treatment and/or cure.
Alicja Copik, University of Central Florida	Generation of highly cytotoxic natural killer cells for cellular therapy of cancers using novel microparticle approach	Stem cell transplantation (SCT) is the current core treatment for many types of blood cancers, including most types of leukemia. Unfortunately, challenges such as the lack of suitable donors for ethnically diverse patients, cancer relapse, and graft-versus-host disease limits their application and success. More than 70% of patients who could benefit from stem cell transplant do not have a matched sibling donor and the chances of finding a matched unrelated donor strongly correlates with ethnic background. Therefore, there is a great need for new and innovative approaches to enhance current therapies or to provide a completely different alternative to SCTs. The goal of this study is to establish a new cell therapy for AML using a type of immune cell called a natural killer (NK) cell. These NK cells will be generated by several different approaches to determine which approach yields a more potent anti-tumor product. Furthermore, a specific type of drug that may enhance the anti-tumor effect of these generated cells will be tested. Tumor cells will also be analyzed to determine how they are able to evade the immune system. In the end, this study is expected to lay foundations for a follow-up Phase-I/II clinical trial of an NK cell-based therapy for blood cancer patients at our institution. This therapy would provide a treatment alternative to disparate groups such as ethnic minorities who do not have a matched donor and elderly who require less rigorous treatments.
Scott Gilbert, University of Florida	Bladder Cancer Outcomes and Impact Study (BCOIS)	Bladder cancer is the fifth most common cancer in the United States and accounts for nearly 70,000 new cases of cancer each year. Florida has the second highest number of bladder cancers diagnosed each year, following only California. Although most bladder cancers are detected at an

		early stage, about 25% of patients present with invasive disease for which bladder removal is recommended. In addition, 15-20% of patients originally diagnosed with a low-stage bladder cancer progress to higher stage tumors that prompt bladder removal at a later time. Approximately 10,000 bladder removals - called cystectomy in medical terminology - are performed each year in the US. Following bladder removal, urine is redirected out of the body in a reconstructive procedure called a urinary diversion. Cystectomy and urinary diversion are associated with long lasting and even permanent changes in physical appearance (most urinary diversions result in a bag worn by patients attached to the outside of their abdomen), body function (for example, incontinence), as well as increase the risk of developing kidney stones, urine infections or impairment in kidney function. To date, there has been relatively little research examining the effects of these changes. The objectives of this study are to assess how common and detrimental those complications are by tracking clinical outcomes as well as surveying patients and their spouses/partners regarding the impact of and adaptation to bladder removal.
Chen Ling, University of Florida	Treatment for human hepatocellular carcinoma based on genome- and capsid-optimized recombinant adeno-associated virus serotype 3 vectors	Human hepatocellular carcinoma (HCC) is associated with ~695,900 deaths worldwide each year. Alternative therapies are still warranted to treat HCC. The main aim of this proposal is to develop novel recombinant adeno-associated virus (rAAV) vectors for the selective and highly efficient targeting of human HCC. rAAV vectors have been succeeded in a number of gene therapy clinical trials, including Leber's congenital amaurosis and hemophilia B. The lack of human disease associated with AAV and helper virus dependence are two major safety features for using rAAV as a gene therapy vector. In previous studies, we have shown that recombinant adeno-associated virus serotype 3 (rAAV3) vectors efficiently infect several HCC cell lines in vitro and HCC tumors in vivo. Meanwhile, the transgene expression can be restricted to malignant cells using human liver cancer specific promoter, such as alpha-fetoprotein (AFP) promoter. In clinic, it is important to target as many malignant cells as possible. To this end, we plan to modify both the

		viral capsid and viral genome to further enhance the infectivity of rAAV3 vectors in HCC cells. Secondly, the capsid- and genome-optimized rAAV3 vectors containing therapeutic genes will be tested for the potential gene therapy of human HCC tumors in murine models in vivo. The proposed studies will lead to a new method to treat human liver cancer patients.
Priyamvada Rai, University of Miami	Implications of Cellular Senescence as a Treatment Response in Prostate Cancer	Prostate cancer is one of the most common cancers to afflict American men and a leading cause of cancer-related deaths.Unfortunately therapeutic options for prostate cancer treatment are limited once the tumors become non-responsive to androgen deprivation therapy (ADT). Development of novel treatment strategies is limited by the lack of knowledge regarding molecular mechanisms that give rise to these non-responsive or androgen-refractory tumors. ADT induces a proliferative arrest rather than cell death in the bulk prostate tumor. Our preliminary data,using cell culture models of prostate cancer,indicate these non-proliferating but viable cells resist cell death and eventually give rise to androgen-refractory cancer cells.Thus we hypothesize interventions that acutely promote cell death instead of non-proliferation under ADT in androgen-responsive prostate cancer cells will inhibit outgrowth of androgen-refractory tumors. Our proposed research addresses this issue by investigating how cell death can be activated by oxidative stresses produced during this initial ADT-induced proliferative arrest(termed cellular senescence), by defining the role of senescence-associated secreted inflammatory proteins in promoting androgen-refractory tumor growth, and by determining whether acquisition of chemoresistance to other clinically relevant senescence-inducing treatments also leads to androgen-refractory traits in prostate cancer cells.
Tongyu Wikramanayake, University of Miami	Laser-accelerated Hair Regrowth after Chemotherapy-Induced Alopecia	In 2012, an estimated 1.6 million people will be diagnosed with cancer in the U.S. More than half of them will receive chemotherapy, and approximately 65% of those (~520,000) will develop chemotherapy-induced alopecia (CIA). CIA is one of the most common side effects of cancer treatment, and has significant negative impact on patients' quality of life, negatively affecting their perception of appearance, body image, sexuality,

		and self-esteem. Patients also worry about the loss of privacy of having cancer because of CIA, and some patients would even consider declining chemotherapy for fear of hair loss. To develop effective treatment for CIA, we recently observed that low-level laser (
James Wilson, University of Miami	FAST Probes: Reporters of Activation States in Cancer Relevant Signaling Pathways	While great strides have been made in detection and treatment of human cancers, there remain unanswered questions related origin, progression and resistance to treatment. Our goal is to develop a toolkit of chemical probes that enable detailed, molecular level investigations of the biomolecular changes associated with many cancers. Our tools, called FAST (Fluorescent Activation STate) probes, will enable researchers to identify populations of cancer relevant signaling biomolecules. We will achieve this goal through 1) the design and chemical synthesis of new probes, 2) screening the probes for binding to cancer relevant biomolecular targets and 3) demonstrating their application in identifying these targets in tumor-derived cell lines. The knowledge gained through the application of these new chemical tools will aid in the development of new chemotherapies and provide better correlation between disease mechanisms and clinical outcomes.
Ravi Shridhar, Moffitt Cancer Center & Research Institute	Validation of a Radiation Response Signature in Borderline Resectable Pancreatic Cancer Patients Treated with Induction Chemotherapy followed by Stere	Pancreatic cancer remains the fourth leading cause of cancer death in the United States. Cures occur with surgical resection leaving no microscopic disease behind (R0 resection) in only 20% of patients. Leaving disease behind (R1/R2 resection) is associated with poor outcome. Such patients do no better than those that are treated with chemotherapy only. Patients are classified as borderline resectable (BR) if the tumor involves the blood vessels running adjacent to the pancreas leaving no separation between which the surgeon can cut. In this setting preoperative chemotherapy and radiation can induce the death of part of the tumor and increase the likelihood of R0 resection. Conventional chemoradiation (CRT) is given in 28 fractions with chemotherapy as a radiosensitizer. High-dose radiation delivered in 5 treatments is stereotactic body radiotherapy (SBRT). We have found that SBRT is as effective as pre-operative CRT. Nevertheless, some patients are completely resistant to radiotherapy. We have developed a gene expression signature that predicts the

		sensitivity to conventional radiation in a variety of tumors. In this proposal our aim is to perform a clinical trial to validate this radiation signature in patients with BR pancreatic cancer which will allow us to predict which patients would most benefit from SBRT and avoid radiation in those who will be resistant. This is an essential first step in developing a personalized therapy for BR pancreatic cancer.
Enrique Mesri, University of Miami	Endothelial progenitor cells in viral oncogenesis of AIDS-Kaposis sarcoma	Kaposi's sarcoma (KS) is an AIDS-associated cancer (AIDS-KS) that is characterized by intense neo vascular formation and uncontrolled growth of spindle shaped cells. The state of Florida, in particular, the South Florida/ Miami area, are among the areas with higher incidence in the United States. Although AIDS KS many times responds to anti-retroviral therapies, in many cases and in its advanced forms, it cannot be cured. KS is caused by a human carcinogenic virus, the Kaposi's sarcoma associated herpes virus (KSHV). The exact molecular and cellular mechanism by which this virus causes cancer is not known. Understanding it could help to develop new therapeutic and preventive approaches to the disease. This grant intends to discover which is the exact cell type that when infected with the KSHV virus will develop Kaposi's sarcoma. Our laboratory has gained important insights and has constructed laboratory tools including new animal models that could make this research possible. Achieving the goals of our research will deepen our understanding of AIDS-KS and will help to prevent and treat this cancer.
Weihong Tan, University of Florida	Development of molecular probes for biomedical applications	A key challenge in treating cancer is the generation of molecular-level tools for diagnostic and therapeutic applications. One such tool is the molecular probe, commonly defined as a group of molecules, or atoms, able to attach to other molecules, or cellular structures, and used to study the properties of those molecules or structures. In our work, we have developed a special molecular probe, termed aptamer (short ssDNA/RNA molecular probes which can be synthesized reproducibly), characterized by its ability to recognize individual cancer cells by homing to proteins and other biomarkers present on the cell surface. The therapeutic and diagnostic potential of aptamers includes discovering cancer-related

		biomarkers, particularly intra- and extracellular proteins, and molecular imaging of diseased cells at the earliest stages. In the proposed work, we will further develop our aptamers for these tasks in the context of a lung cancer model. Once completed, this proposal will show the wide biomedical and bioanalytical applicability of aptamer-based diagnostics/therapeutics, and we will convincingly demonstrate how the properties of aptamers can be used to overcome the difficulties that current methodologies fail to adequately address in cancer related research and treatment.
Hendrik Luesch, University of Florida	Development of scale-up synthetic method for apratoxin S4, a novel drug for the treatment of colorectal cancer	Natural products show outstanding potential as starting points in drug discovery, especially in the quest for anticancer drugs. We have discovered that the marine natural products called apratoxins have anticancer properties; however, the original compound had some toxic side effects. We have generated a new apratoxin (apratoxin S4) that lacks the toxic side effects of the natural product. We aim to generate large quantities of this improved apratoxin, which is necessary for further drug development. Our goal is to demonstrate the feasibility of large-scale chemical synthesis to generate enough apratoxin S4 for extensive preclinical testing.
John Copland, Mayo Clinic	Stearoyl CoA as novel molecular target for treatment of kidney cancer	Kidney cancer remains on the increase in the United States with about 64,770 new cases of kidney cancer in 2012 and about 13,570 people will die from this metastatic disease. Current FDA approved drugs for metastatic disease give months of survival benefit but all patients develop drug resistance. There is a dire need for more effective treatment for metastatic kidney cancer. We have discovered a new gene, stearoyl CoA desaturase 1 (SCD1) that causes kidney tumors to grow. We have identified inhibitors of SCD1 and plan to develop a SCD1 inhibitor as a new treatment for kidney cancer. We have also discovered that an SCD1 inhibitor when combined with an FDA approved drug (a mTOR inhibitor) for kidney cancer results in increased tumor death and antitumor synergy. Thus, our goal is develop this new inhibitor as a combinatorial therapy for kidney cancer. We also will develop an assay which will detect SCD1 in kidney cancer tissues. This detection assay will be used as a diagnostic

		indicating that a patient should be treated with a SCD1 inhibitor. Our team includes an oncologist who specializes in treating kidney cancer and clinical trials. As a result of our research, we foresee clinical trials towards this new treatment strategy that should increase the survival benefit of patients diagnosed with the most common form of kidney cancer.
Branko Stefanovic, Florida State University	Controlling Fibrosis to Prevent Hepatocellular Carcinoma	The major type of liver cancer is hepatocellular carcinoma (HCC). It is the 5th most common cancer and the 3rd leading cause of deaths among cancers. When diagnosed, patients have average survival of 9 months. There is no cure for HCC other than liver transplant. 90% of HCCs appear in cirrhotic livers, making cirrhosis essentially a precancerous state. Prevention or attenuation of liver cirrhosis can greatly decrease the incidence of HCC. However, there are no antifibrotic drugs to treat cirrhosis. Hepatic stellate cells (HSCs) produce type I collagen in liver fibrosis, and type I collagen is the protein responsible for development of liver fibrosis and cirrhosis. We have discovered one chemical compound (60D17) that can dramatically decrease type I collagen synthesis. The compound has been tested for inhibition of collagen synthesis by HSCs. 60D17 is a candidate antifibrotic drug that we want to bring to clinical trials. The first goal of this proposal is to test the efficacy of this compound in an animal model of liver fibrosis. We obtained 8 derivatives of the 60D17 compound with the similar core structure, this modifications may increase its potency. The second aim of the proposal is to test the 60D17 derivatives for collagen inhibition in HSCs and, if a more potent derivative is found, to test it in an animal model of hepatic fibrosis. The long-term goal is to develop a specific antifibrotic drug that is effective in reducing liver fibrosis and the incidence of HCC.
Pearlie Epling-Burnette, Moffitt Cancer Center & Research Institute	Verification of TERT assay for MDS diagnosis	This application focuses on development and commercialization of a novel diagnostic assay for Myelodysplastic Syndromes (MDS), which is the most frequently occurring blood malignancy in the United States. The disease causes changes to the bone marrow, which is where blood cells are made. The diagnosis is based on subjective changes in cell shape and is complicated because multiple tests are needed. Our results have

		defined MDS to have a deficiency in a protein that maintains the ends of chromosomes called telomerase reverse transcriptase (TERT). Comparing cases and controls, we found a threshold that is able to differentiate between these two groups with 92% accuracy. Additional studies are needed to develop the assay and to attract investors. In this application, we propose specific aims necessary to advance the developmental potential of this product. Specific aim 1 will determine the sensitivity or the effectiveness of the test to differentiate patients with bone marrow biopsy-confirmed MDS from healthy controls. Specific aim 2 will determine the specificity, or the extent to which the test gives negative results in those that are free of the disease. With a team of experienced leaders in the field of commercial diagnostics, this proposal is sure to assist with advancing the marketability of the product within the funding period.