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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Helen M. Bramlett, Ph.D.	University of Miami	Whole Body Vibration Improves Stroke Outcome in Nicotine-exposed Rats	Millions of smokers are disabled as a result of stroke and ischemic stroke accounts for almost 85% of total stroke cases. Ischemic stroke occurs when the blood supply to part of the brain is disrupted due to thromboembolic occlusion of a cerebral artery. Disruption of blood supply to part of the brain causes focal ischemia damaging the cortical region initially. To date, the only drug that has been approved to treat acute stroke is the clot-dissolving drug tissue plasminogen activator (tPA). However, tPA must be administered within 3 hours of the onset of an ischemic stroke, which makes it a viable treatment for less than 15% of stroke patients. Thus, new therapies for acute stroke with extended therapeutic windows are badly needed. Physical therapy and exercise have been shown to be beneficial for recovery but often are not an option for frail patients. Whole Body Vibration (WBV) mimics the internal forces exerted on by exercise, and can be effectively incorporated in any patient's treatment regimen. Although WBV has been previously shown to be beneficial in maintenance and increase of bone mass, in this study we want to test its direct application in the recovery from stroke. We hypothesize that WBV will significantly improve cognition, inflammation and neuron growth in nicotine exposed rats after stroke.

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Christine Chung, M.D.	H. Lee Moffitt Cancer Center and Research Institute	Molecular Signatures of Immunotherapy Response and Improved Survival in Tobacco-related Head and Neck Cancer	Head and neck squamous cell carcinoma (HNSCC) remains one of the most devastating cancers affecting oral cavity, oropharynx, hypopharynx, and larynx that are critical structures for life's most essential functions such as eating, breathing, and talking. Common risk factors are tobacco and alcohol use and human papillomavirus (HPV) infection. The patients with tobacco-related HNSCC have the worst prognosis compared to the HPV-related HNSCC. Even within the HPV related HNSCC, patients have worse outcome if they have history of smoking compared to nonsmokers, demonstrating the devastating effects of tobacco use in cancer development, treatment resistance and cancer-related death. Recently immunotherapy has become a promising therapeutic option in HNSCC. Among the numerous immunotherapeutic agents, programmed cell death-1 (PD-1) inhibitors are the most advanced in development in HNSCC, particularly pembrolizumab and nivolumab. PD-1 is an important protein that regulates the immune cell functions which are critical in recognizing and eliminating the abnormal cancer cells. Activation of PD-1 can decrease this immune function by suppressing T cells. Thus, inhibiting PD-1 improves the ability of T cells to fight the cancer. These immunotherapy agents set themselves apart from chemo- and other therapies by their ability to induce long lasting clinical benefits leveraging the patient's own immune system; however, the efficacy is seen only in a limited number of patients. Only 13-18% of HNSCC responds to these agents, and long term toxicities have not been fully defined because it is very new treatment approach. It is imperative to identify patients who will truly benefit from these immunotherapy agents, to improve the current response to immunotherapy, and accurately assess the toxicities as we move towards more personalized therapies. In this project, we propose; 1) to identify predictive biomarkers to select the patients who will benefit the most from current PD-1 inhibitors based on their tumor genetic alterations that may trigger the immune response, 2) to determine whether combining cetuximab, a currently FDA-approved cancer drug, and nivolumab will improve the immune response and clinical benefits, 3) to determine changes in the tumor infiltrating immune cells induced by tobacco use, 4) to determine changes in the tumor genes and proteins induced by tobacco use in order to find new drug targets, and 5) to develop a smartphone-based assessment for real-time reporting of toxicities and tobacco use by the patients between the clinic visits. The findings from this project will have a significant impact in the health of Floridians by reducing mortalities through improving the selection of patients who will gain the most benefit from receiving PD-1 inhibitors, reducing mortalities by a novel combination therapy, and reducing morbidities of treatment-related toxicities and on-treatment tobacco use through development of a real-time assessment by patient reporting.

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W. Dalton Dietrich, Ph.D.	University of Miami	The Therapeutic Effect of P7C3-A20 on Stroke	Focal cerebral ischemia leading to stroke is a devastating condition that has few therapeutic interventions available except for early thrombolytic therapy or new catheter-based endovascular strategies. During severe cerebral ischemia, cells deplete their oxygen and energy reserves, leading to neuronal cell death and prolonged behavioral deficits including motor and cognitive impairments. There is therefore a major need to develop and test new pharmacological agents to protect neurons from irreversible cell death. In addition to cell death, several studies have reported an increase in the generation of new neurons in specific brain regions following focal cerebral ischemia. This cellular response is believed to potentially provide an endogenous repair mechanism that could improve outcome by replacing injured neurons. However, the majority of these newly formed cells undergo cell death. Therapeutic strategies that also protect these newly formed neurons for death would potentially promote functional recovery after stroke. The recently identified proneurogenic compound P7C3-A20 has been reported to inhibit neuronal cell death, enhance the formation of new neurons and improve cognitive function in several neurodegenerative models. The goal of this project is to determine for the first time whether treatment with P7C3-A20 at various periods after the focal ischemic insult would decrease overall brain pathology, reduce the death of the newly formed neurons and improves long term motor and cognitive function. Proposed studies will investigate the therapeutic window for treatment effects and clarify a potential causative role of new neuron cell survival in the improved outcomes. To conduct this study, a transient middle cerebral artery occlusion model in rats and mice will be used to examine sensorimotor and cognitive behavioral outcomes over chronic survival points. The generation of new neurons after focal ischemia will be examined in two distinct areas of the brain (subgranular and subventricular zones) that are known to demonstrate neurogenesis after injury. Special staining approaches will be used with novel tissue clearing technique combined with 3-dimensional reconstructions to resolve cellular responses to injury and treatment. Finally, a special transgenic mouse model (Nestin-TK-GFP) will be used to independently manipulate the degree of neurogenesis and determine a causal link to improved functional outcomes. We will make use of established research guidelines to reduce experimental bias and enhance reproducibility of findings. The major endpoints of the proposal are therefore to determine if P7C3- A20 is a viable therapeutic strategy after experimental focal ischemia and to clarify potential mechanisms of action including enhanced neurogenesis. Importantly, if found to be effective, this neuroprotective treatment could be combined with available endovascular approaches to maximize protection and recovery.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Jhanelle Gray, M.D.	H. Lee Moffitt Cancer Center and Research Institute	Targeting Immunosuppressive Cancer Associated Fibroblasts and Immune Checkpoints in NSCLC	Lung cancer causes more cancer deaths than breast, colon, prostate, and pancreatic cancer combined. It is an immunotherapeutically responsive cancer. Immune checkpoint inhibitors, including anti-PD1/PD-L1 therapies, produce improvements in median overall survival from 12 to 24 months, with some durable responses. As dramatic as these results are, less than half of patients benefit. There are many other mechanisms that may suppress the immune system, including in the tumor microenvironment, which can lead to escape from tumor killing by immune cells. Combination strategies that interfere with the different immunosuppressive mechanisms operational within the tumor microenvironment are of interest in lung cancer immunotherapy. We recently discovered that the agent nintedanib (FDA approved for idiopathic pulmonary fibrosis; approved in Europe for combination with chemotherapy in lung cancer), which blocks multiple receptors including fibroblast growth factor receptors, has the potential to be repurposed as an anti-cancer immunotherapeutic, abolishing the immunosuppressive influence of cancer-associated fibroblasts (CAFs). CAFs are the most prominent cell type in the tumor stroma and differ from normal fibroblasts as they are continuously activated. At Moffitt (Antonia Lab), we developed a technique to grow out CAF cell lines made from human lung cancer tumors. In this model, T cells are strongly inhibited in the presence of CAFs due to expression of immune checkpoints and other immunosuppressive enzymes. Based on our preclinical work and the literature (which support our findings), we hypothesize that targeting immunosuppressive CAFs within the tumor microenvironment in combination with immune checkpoint blockade with nivolumab may translate into better tumor control. Our project is unique and innovative in that, while many studies are solely evaluating various checkpoint inhibitor combination strategies, we recognize the importance and have provided a novel, rational, feasible and scientifically sound approach to also target a unique source of immunosuppression within the tumor microenvironment. The significance of this project is that by immune suppression blockade, we are primed to increase the immune-mediated tumor responses, identify markers that can better predict tumor shrinkage while reducing waste and toxicity (precision medicine), and enrich patient treatment algorithms and ultimately improve outcomes for patients with nonsmall cell lung cancer. With these goals in mind and based on the above, we developed a phase IB/II clinical trial with serial blood collections and tumor biopsies to evaluate the combination of nintedanib with immune-checkpoint blockade (nivolumab). Objective #1. To determine the safety and efficacy of nivolumab plus nintedanib in advanced lung cancer. Objective #2. To correlate key markers obtained from serial tumor biopsies and blood collections with response to treatment. Objective #3. To correlate key markers obtained from serial tumor biopsies with resistance to treatment.

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Zhihua Jiang, Ph.D.	University of Florida	Mechanisms for Tobacco Smoke to Modulate Aortic Aneurysm Development	Aortic aneurysm stands as the 15th leading cause of death in the United States. This aortic disease affects 5% of the general population, with the incidence being 3-5 times higher in smokers than in non-smokers. Furthermore, tobacco-use doubles the rate of aortic dilation and the risk of rupture. Although quitting tobacco has proven benefits of halting further escalation of the aortic aneurysm, yet around 42 million Americans continue to smoke. Currently, mechanisms underlying tobacco smoke-exacerbation of aortic aneurysms are poorly understood. Strategies capable of reducing or eliminating the deleterious effect of tobacco smoke on aortic aneurysm development remain unavailable. Studies for lung cancer and chronic obstructive pulmo-nary disease have generated rich knowledge about the impact of tobacco smoke on the biology of endothelial cells, smooth muscle cells (SMCs), and immune cells. A commonly held view is that tobacco smoke impairs the body's defense mechanisms via suppressing the function of the immune system, provoking dysfunction and death of endothelial cells, and accelerating proliferation of SMCs. However, this theory cannot explain the clinical presentation of aortic aneurysms where intense inflammatory infiltrates are located across the aortic wall and fewer SMCs are present in the tunic media. A large body of clinical and experimental evidence supports the concept that aortic aneurysm is an inflammatory disease. Recent advances in immunology have identified two different types of inflammation, with each type of inflammation driven by a distinct subset of immune cells and cytokines. Specifically, the type 1 inflammation is governed by a subset of Tcells, called type 1 T helper or TH1 cells whereas the type 2 inflammation is dominated by TH2 cells. Under physiological conditions, the function of TH1 and TH2 cells is well-balanced to maintain tissue homeostasis. Interestingly, epidemiological investigations have shown that compared with the general population, diabetic patients are two times less likely to develop aortic aneurysms while asthma pa-tients are at a 2 times greater risk of developing aortic aneurysms. A detailed characterization of the immune system of these patients has uncovered that diabetic patients have a TH1-baised immunity whereas asthma patients have a TH2-biased immunity. These studies have established a correlation of aortic aneurysm formation with the TH2-biased immune responses. As opposed to the traditional belief that tobacco smoke suppresses the immune function, emerging evidence suggests that it skews the TH1/TH2 balance toward a TH2 phenotype. This finding has provided a plausible explanation to the protective effects of diabetic condition and the detrimental effects of asthma on aortic aneurysm formation. It appears that tobacco smoke exacerbates aortic aneurysms via shifting the TH1/TH2 balance to a TH2 phenotype. In this project, we will use both genetic and pharmaceutical approaches to test this hypothesis. Results generated in this project will not only deepen the mechanistic understanding of tobacco ex-acerbation of aortic aneurysms but also provide information on the potential of FDA approved immune-modulators to eliminate the deleterious effects of tobacco smoke on aortic aneurysm development.

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Mandip S. Sachdeva, Ph.D.	Florida A&M University	Oral Nanotechnology in Triple Negative Breast Cancer	An estimated 1 million cases of breast cancer are diagnosed annually worldwide. Of these, more than 170,000 are described as triple-negative. Triple-negative breast cancer (TNBC) is defined by the lack of protein expression of estrogen receptor (ER) and progesterone receptor (PR) and the absence of HER2 protein over-expression. The complex nature of tumors represents a significant challenge to the health care system. Triple Negative Breast Cancer (TNBC) does not have a first line treatment. Development in this area will help many patients' especially the African American population which is disproportionately afflicted by it. Majority of the therapy is done in clinics by intravenous administration which involves repeated hospital visits and is cumbersome for patients. Development of an oral nanoparticle product of an already existing drug (Docetaxel which is given intravenously) in combination with another agent (Piperlongumine), which can significantly potentiate its activity in a synergistic manner against TNBC, will be of immense help to cancer patients allowing them to avoid the adverse effects involved with multiple parenteral injections and also avoid the need to go to the hospital. The ultimate goal in this proposal is to develop an oral nanoparticle capsule based formulation for the treatment of triple negative breast cancer with minimal toxicity and enhanced efficacy.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Julie Y. Djeu, Ph.D.	H. Lee Moffitt Cancer Center & Research Institute	Nanoparticle-based targeting of miR183 for immunotherapy of lung cancer	This application offers a new approach to lung cancer immunotherapy that has never been tried before. It is based on our novel observations of immune suppression in the tumor microenvironment. Circulating immune cells function to survey the body for abnormal cells and a type of immune cells, called natural killer (NK) cells are especially potent in seeking out tumor cells through multiple receptors that only bind unique proteins that appear on nascent tumor cells. These receptors utilize a key protein called DAP12 to anchor to the NK cell surface. However, we find that tumor cells produce a protein called transforming growth factor-b that can disrupt NK cell function by depleting DAP12. This is accomplished by activation of a microRNA, miR183 that specifically binds to the DAP12 gene to destroy it. Therefore NK cells cannot display their receptors on the cell surface and become blind to the surrounding tumor cells, allowing tumor cells to escape immune detection. We also find that nicotine from tobacco smoke, long associated with lung cancer development, can activate the same mechanism in NK cells. Without immunity, cancer cells can grow unchecked. This is the first report of a microRNA that controls immune cells in lung cancer and the targeting of this microRNA presents a highly innovative and new strategy to treat cancer. Before attempting this therapeutic approach in man, it is critical to first obtain proof of concept in mice. We have established a working model in immunodeficient NSG mice which can accept human tumors and human NK cells. Human NK cells, if implanted in mice the same time as the tumor, can readily eliminate the tumor, but if implanted after the tumor has grown for a week, an immunosuppressive environment is already established that renders NK cells impotent. This model recapitulates what is occurring in human cancer patients and will be used to test formulations of anti-sense miR183 to treat lung cancer. Nanoparticles, made of poly(lactide-co-glycolide) (PLGA) that have long been in medical use in dissolvable sutures and proven safe, will be used to deliver anti-sense miR183. These nanoparticles will then be injected into human tumor-bearing mice along with human NK cells to evaluate if NK cell recovery is obtained. To optimize the nanoparticles to reach NK cells in the tumor bearing mice, we will functionalize them with NK homing molecules and facilitate their entry into the NK cells by attaching cell penetrating peptides to the nanoparticles. If efficacy is demonstrated with these nanoparticles, this method would revolutionize the treatment of lung cancer. Moffitt Cancer Center is poised to conduct these trials because it has an outstanding immunotherapy research program and admits about 800 new lung cancer patients annually. Several advantages are associated with such nanoparticles. They can serve as off-the-shelf reagents and it can be administered not only to any lung cancer patient, but also to patients of other tumor types. It is well accepted that immune escape is a hallmark of all cancers and our product could be a universal anti-cancer agent.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
David J. Drobes, Ph.D.	H. Lee Moffitt Cancer Center & Research Institute	Facilitating Smoking Cessation with Reduced Nicotine Cigarettes	Cigarette smoking remains the top avoidable cause of death and disease in Florida, responsible for most cases of lung cancer, as well as many other cases of cancer, heart disease, pulmonary disease, and diabetes. Despite the state-supported availability of multiple avenues for smoking cessation (e.g., telephone counseling, web-assisted cessation, in-person counseling, free nicotine replacement therapy), only a small percentage of smokers within Florida avail themselves of these treatment options, and approximately 18% of Floridian adults continue to smoke. Research over the past several decades has shown that long-term cessation rates with even the most intensive interventions rarely exceed 20-30%. Thus, it is vital that additional research be conducted to develop and validate novel methods for effective smoking cessation. It has long been understood that nicotine is the primary constituent in cigarettes and other tobacco products that supports the initiation and maintenance of an addiction to tobacco. The recent availability (via the NIDA Drug Supply Program) of research cigarettes with varying levels of nicotine creates a unique opportunity to evaluate the potential benefits of very low nicotine content (VLNC) cigarettes as a new tool for smoking cessation. In that vein, the proposed research will develop and test a novel smoking cessation strategy, based on theory and research concerning extinction. Specifically, this theory-driven intervention will be designed to extinguish the expectation of reinforcement from smoking via pre-quit smoking of VLNC cigarettes. In turn, this should result in a higher likelihood of successful quitting. First, our experienced research team and consultants will adapt and refine intervention materials, in order to provide smokers with clear and detailed instructions for smoking VLNC cigarettes prior to quitting, in a manner that will maximize extinction to smoking-related reinforcement. This intervention development process will involve expert review and recommendations, and will incorporate feedback from smokers (n=20) enrolled in a pilot study of the intervention. The pilot study will also examine the feasibility of the targeted intervention, along with two tapering schedules (immediate vs. gradual) for transitioning to VLNC cigarettes over a 4-week pre-quit period. Next, a randomized controlled trial (RCT; n=200) will compare effects of the targeted intervention vs. a standard intervention, in combination with the two tapering schedules, on smoking cessation outcomes. In addition, two behavioral paradigms will be administered to RCT participants, to determine intervention effects on smoking behavior in a short-term laboratory Smoking Analogue tasks and a 5-day abstinence challenge task. Finally, analyses will explore if the treatment works better for particular types of smokers, and if the treatment effects on smoking cessation outcomes are mediated by effects on related variables (e.g., decreased nicotine withdrawal or cravings to smoke). This information will be particularly useful for determining which smokers may benefit most from this smoking cessation approach, and for better understanding how this form of treatment works.

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Daiqing Liao, Ph.D.	University of Florida	Pharmacologic inhibition of acetyltransferase CBP/p300 as a new therapeutic approach for breast cancer	Although effective therapies exist for breast cancer (BC), many patients do not derive clinical benefits from current standard of care treatments such as endocrine therapies for estrogen receptor-positive (ER+ subtype), trastuzumab for HER2-enriched BC, and chemotherapies for the triple-negative (TNBC) subtype. Therefore, it is imperative to identify new therapies that increase response rate to current therapies and overcome drug resistance. ER depends on coactivators to activate gene expression underlying tumor growth. CBP (also called CREBBP) and p300 are key ER coactivators, and found to be overexpressed in the majority BC cases. By assisting ER and other oncogenic proteins, CBP/p300 are active in cancer cells of all BC subtypes, and thus pharmacologic inhibition of CBP/p300 should suppress the growth and progression of primary breast tumors of all BC subtypes. Candidate drug compounds that target CBP/p300 have been identified in our preliminary studies and will be tested for their effectiveness in suppressing tumor growth and metastasis of major BC subtypes. Importantly, we will determine whether the new agents can enhance therapeutic effects of endocrine therapy (e.g., tamoxifen), chemotherapies (e.g., docetaxel) as well as HER2-targeted therapies (e.g., trastuzumab). Patient safety is of paramount concern for any drug development effort. Therefore, the safety and pharmacologic properties of new CBP/p300 inhibitors will be stringently assessed to ensure that they will be suitable for clinical use. These novel agents, specifically targeting CBP/p300, should be effective for suppressing the growth and metastatic progression of primary breast tumors. The new inhibitors are small-molecule compounds and are thus suitable for various systemic treatments, such as via oral administration. Drugs that target CBP/p300 have not yet been developed, and thus new agents emerging from this project could have an unprecedented impact on treating BC, contributing to the ultimate goal of ending breast cancer.

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Maria Jose Miguez, M.D., Ph.D.	Florida International University	Biobehavioral Intervention For Smokers Living With HIV	While substantial progress has been made in reducing smoking prevalence to 20% among the general population, smoking ranks among the top preventable causes of death and disease in Florida. Unfortunately, these statistics are even more grim for people living with HIV. The smoking rates among this population are two to four times higher, thus increasing the risks of numerous diseases and threatening health gains achieved with antiretroviral treatment. As a result, PLWH receiving ART lose more years of life to smoking than to HIV, with mortality tripling compared to the background population. Unfortunately, research on smoking cessation interventions for PLWH has been scarce and has provided disappointing results. Thus, the long-term goal of this program is to develop a tailored intervention that can be readily integrated into HIV treatment settings. Such research is critical given that Florida remains the epicenter of the HIV/AIDS epidemic in the United States. Our formative work indicated that people living with HIV receiving antiretroviral therapy exhibited significantly higher levels of plasma nicotine. These heightened levels may be hampering smoking cessation efforts and success rates. The overall objective of the trans-disciplinary team of HIV/tobacco funded researchers is to test if tailoring nicotine replacement doses to temper these excessive levels will enhance the efficacy of the intervention. This will be accomplished by: 1) assessing pre-trial plasma levels, 2) determining participant genotype (which to our knowledge has not been used in cessation studies among PLWH) , and 3) providing tailored feedback to the participants based on the assumption that the higher the knowledge and perception of risk the higher the interest in modifying risky behavior(s). To test our proposed model based on proven smoking prevention and control methods, 500 PLWH ready to quit smoking will be enrolled in a double-blind, randomized clinical trial with intent-to-treat design. We will be comparing a standard, well-validated, brief smoking intervention that follows NCI guidelines and will consist of brief advice + nicotine replacement therapy (NRT) versus the tailored one (brief smoking intervention + personalized doses of NRT). The primary outcome for this study will be the rates of smoking cessation, point prevalence abstinence (prior 7 and prior 30 days), and verified continuous abstinence 3-, 6-, and 12-months post scheduled quit day. Building on the strengths of the SHARC center funded by NIAAA, and our FILTERs center funded by the Florida Department of Health, the knowledge gained here could potentially contribute a more complete bio-behavioral model to the intervention field. The proposed study, if successful, will provide a new tailored, replicable, and manual-based intervention for people living with HIV. It can also provide much needed information about the key mediators and moderators of smoking cessation interventions in this vulnerable population. Our long term goal is to reduce the burden of one of the most devastating causes of morbi-mortality in our time and improve overall quality of life. The study could also pave the way for the future development of tailored smoking interventions for other populations (e.g., menthol users, older women, adolescents, older adults).

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Jong Park, Ph.D., M.P.H., M.S.	H. Lee Moffitt Cancer Center & Research Institute	Biobank for African American Prostate Cancer Research in Florida	Prostate cancer disproportionally affects men of African Ancestry (AA) who have much higher incidence and mortality rates than Caucasian men. In the state of Florida, approximately 2,000 AA cases were reported every year according to the Florida Cancer Data System (FCDS) of the Florida Department of Health. The relationship between risk of prostate cancer and smoking is a matter of debate. However, male smokers have higher level of blood male hormones, thus androgens, which may increase prostate cancer risk and progression. Recently, a large study with more than 20,000 prostate cancer patients found a consistent risk (11-22%) increase for prostate cancer among current smokers. Moreover, significant increase of risk (24-30%) for advanced prostate cancer, such as lethal cases, was observed among current smokers. We agree on the urgent need for a statewide biobank to support prostate cancer research among men of African Ancestry in Florida. It has not been initiated due to various reasons, such as limited resources to establish the infrastructure for collaborative data and biospecimen collection. Successful completion of this proposed project will lead to the development of an extremely valuable research asset for health disparity studies for prostate cancer. We anticipate this resource will contribute not only to generate important scientific findings but also allow researchers to leverage additional national funding, such as NIH, or DOD and ultimately lead to better strategies to reduce prostate cancer incidence and mortality. We will also investigate the effect of smoking on aggressiveness of prostate tumor by various mechanisms. For example, we and other investigators previously reported that smoking causes mutations in various tumor suppressor genes, influencing molecular pathways to change behaviors of tumor and increased cancer progression. We will address the shortcomings of these efforts with a systematic recruitment of all AA prostate cancer patients (n=6,000) who diagnosed between Jan 2013 and Dec. 2015 using a well-organized protocol, which was guided by FCDS and our research team.

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Jang-Yen Wu, Ph.D.	Florida Atlantic University	Granulocyte colony-stimulating factor (G-CFS) gene therapy for stroke	Granulocyte colony-stimulating factor (GCSF) is a FDA-approved drug for enhancing hemopoiesis. In addition, we as well as others have shown that GCSF has neuroprotective and neurogenesis properties in animal models of stroke and other neurodegenerative diseases, e.g., Parkinson's disease. Protein therapy using GCSF is attractive because GCSF is well tolerated after systemic delivery. However, its plasma half life is about 4 hours; moreover, there is potential for chronically elevating white blood cells during repeated delivery. Also, no reliable monitoring system is available to follow the progression of stroke treatment. Here we propose one alternative approach which is to administer well regulated GCSF gene delivered by a viral vector –namely a replication deficient adeno-associated virus (AAV) in conjunction with a non-invasive imaging system for monitoring delivery and expression of GCSF in the brain. Recently we have developed an innovative MRI technology which comprises a phosphorothioate-modified antisense (AS) oligo DNA (sODN) to hGCSF which is conjugated to a superparamagnetic iron oxide nanoparticles (SPION) known as hGCSF-AS-sODN-SPION probes and demonstrated that increased expression of hGCSF is associated with increased survival rate in BCAO stroke mice model (Gene Therapy, doi:10.1038/gt. 2015.81; 24July, 2015). Specifically, the following specific aims will be addressed: Aim 1 – We will deliver GCSF gene using AAV-CMV-hGCSF or AAV-CMV-HRE-hGCSF vectors in mice BCAO stroke model as well as in cell cultures stroke (hypoxia) model and to determine the mode of neuroprotective function of expressed GCSF. Aim 2 - To further elucidate the mechanism of expressed GCSF in neurogenesis. The significance of this project is that we have already demonstrated the proof of concept of GCSF gene therapy for ischemic stroke. Furthermore, it is highly feasible that the proposed work will lead to securing a patent and that it may facilitate its eventual commercialization and clinical use for stroke treatments.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Monica Webb Hooper, Ph.D.	University of Miami	Addressing Racial/Ethnic Tobacco Health Disparities via Group Intervention	The importance of reducing tobacco-associated health disparities between cannot be understated. Racial/ethnic minorities are less likely to quit smoking, and tend to have elevated stress and depressive symptoms, which may contribute to cessation disparities. Cognitive behavioral therapy (CBT) for cessation addresses these concerns and has the potential to reduce/eliminate disparities. Our preliminary research found racial/ethnic differences in baseline perceived stress and depressive symptoms. Following CBT, these differences were no longer present. Moreover, compared to Whites, African Americans exhibited blunted hypothalamic-pituitary-adrenal (HPA) axis functioning. This RCT will be the first to test the impact of CBT on smoking cessation disparities. Our specific aims are to: (1) Examine the effects of CBT on perceived stress and depressive symptoms in a racially/ethnically diverse sample; (2) test the efficacy of CBT for eliminating smoking cessation disparities; and (3) examine physiological distress as an underlying mechanism for the effects of CBT on racial/ethnic minority smokers (exploratory). We expect that CBT will eliminate racial/ethnic differences in stress and depressive symptoms, and smoking cessation compared to the general health education (GHE) control group. We also hypothesize that HPA functioning will mediate the effect of CBT on smoking cessation, particularly among racial/ethnic minorities. We will randomly assign African American/Black, Hispanic, or White smokers to CBT or GHE, and provide transdermal nicotine patches (TNP) to both intervention groups. Assessments will occur at the end-of-therapy (EOT), and 3, 6, and 12-months. Our primary abstinence outcome will be smoking cessation over the previous 7 days. We will also examine the effect of CBT on TNP adherence. This study has implications for eliminating disparities in psychosocial factors related to smoking cessation, and disparities in quitting success. Addressing stress and depressive symptoms through CBT may facilitate cessation, particularly among racial/ethnic minorities.

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Matthias Salathe, M.D.	University of Miami	Adverse Airway Effects of Inhaled Nicotine from Tobacco and E-cigarettes	In healthy persons, the lungs and airways are cleared from dust, viruses and bacteria to prevent disease development. Cigarette smoke impairs these host defense systems, allowing mucus build up, which is revealed by cough productive of phlegm and associated with frequent infections. This leads to diseases called chronic bronchitis and COPD. From a public health perspective, smoking cessation is therefore an important goal. To try to decrease nicotine craving during smoking cessation, tobacco-free nicotine delivery devices such as electronic cigarettes (ECs) are used. However, the safety of inhaled nicotine via ECs is unknown. In the present study, we will first use human cells that represent the airway surface in a dish and expose them to smoke to study the mechanism by which smoke components, especially nicotine, cause changes leading to increased sputum production. Our preliminary results show that the inflammatory molecule TGF-β1 is responsible for many of these changes and that inhibition of this molecule's signaling can prevent mucus build up. We will test whether nicotine directly or delivery via ECs causes changes similar to tobacco smoke in vitro. Next, we will examine whether changes observed in vitro also occur in vivo in human beings. We will test whether subjects who quit smoking with ECs show toxic effects from nicotine delivered to their airways or whether such a strategy is safe. Therefore, this translational research project will examine treatments to reverse smoking effects on the airway epithelium and will comprehensibly examine whether the delivery of nicotine via ECs has detrimental effects as well. The outcome of this project will not only be important for subjects with smoke-induced lung diseases, but will also provide a decision making basis for subjects and policy makers how to use and regulate nicotine delivery devices such as ECs.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Vani Nath Simmons, Ph.D.	H. Lee Moffitt Cancer Research Center	Expanding the Reach of a Validated Smoking-Cessation Intervention: A Spanish-language Clinical Trial	Tobacco smoking is the leading preventable cause of cancer mortality. Pharmacotherapy and behavioral counseling have demonstrated independent and additive effects on smoking cessation rates; however, counseling is rarely chosen by smokers. Minimal self-help interventions, such as smoking cessation booklets, have very high potential reach, yet have shown low efficacy, with the exception of the extended self-help smoking interventions developed by our research team. Originally developed to prevent post-cessation relapse to smoking, these booklets titled, Forever Free, significantly reduced smoking relapse through two years of follow-up among individuals who had recently quit smoking and were extremely cost-effective. Based on its efficacy and cost-effectiveness, we expanded the intervention to assist current smokers with initial smoking cessation as well as relapse prevention. Our recently completed National Cancer Institute funded trial of this intervention titled, Stop Smoking for Good, revealed high efficacy through the 24-month follow-up, further supporting the utility of extended self-help for promoting and maintaining tobacco abstinence. Availability of a validated Spanish-language version would enhance its public health impact by reaching the largest and fastest growing ethnic minority population of smokers. Although the current smoking prevalence among Hispanics (12.5%) is lower than non-Hispanic whites (18.1%), higher prevalence is observed among certain subgroups (e.g., Puerto Rican males, 35%). In Florida, the smoking prevalence among Hispanics (15.1%) is greater than the national prevalence, and it is higher among subgroups and within medically underserved communities. Prior work has demonstrated that Hispanic smokers face unique challenges such as lower awareness and acceptance of pharmacotherapies and less cessation assistance from health providers. This study goal is to expand the reach of our evidence-based, self-help intervention by developing and testing a Spanish-language version. This would represent an easily disseminable, low-cost intervention with significant public health impact for Hispanic smokers in Florida and elsewhere.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Frederic J. Kaye, M.D.	University of Florida	First-of-its-Kind Intralesional Delivery of Oncolytic therapy for Limited Stage Small Cell Lung Cancer	Small cell lung cancer (SCLC) is a unique and highly aggressive subtype of lung cancer that rapidly spreads to distant organs and for which there have been no improvements in standard treatments for the past 3 decades. SCLC is also the subtype of lung cancer that is most tightly linked with tobacco use and will kill almost 26,000 patients in the U.S. in 2013. Therefore, there is a great need for new therapeutic strategies. We now propose a new team science project to exploit Myxoma virus (MYXV) as a novel viral-based therapeutic that is harmless for normal human tissues but targets and kills SCLC. Projects 1 and 2 will take advantage of our unique resources of i) a large collection of human SCLC tumor samples for testing and optimizing the killing of tumor cells in the laboratory and in specialized animal models, ii) a new genetically engineered SCLC mouse model for further confirmation of safety and efficacy testing, iii) our expertise in optimizing MYXV to enhance immune-mediated cell killing to maximize our ability to cure this disease, and iv) our promising preliminary data already showing efficient MYXV infection and cell killing of human and mouse SCLC in vitro and in vivo. Project 3 focuses on a pioneering clinical program in navigational and interventional bronchoscopy that is only available at the University of Florida and which allows for studying the efficacy of MYXV on fresh SCLC samples with plans for future investigator-initiated clinical trial using intralesional delivery of this therapy. We are making a strong effort to develop tobacco-related SCLC as an important topic for clinical and translational research in the state of Florida.

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Chen Liu, M.D., Ph.D.	University of Florida	Novel Small Molecules for Alpha-1 Antitrypsin Deficiency	The alpha-1 antitrypsin (AAT) deficiency is a common genetic disease with pulmonary emphysema and chronic obstructive pulmonary disease (COPD), for which there is no effective treatment. Smoking tobacco is the single most important risk factor to accelerate the lung disease. The fundamental pathological process is that the accumulation of mutant AAT in the form of polymers within hepatocytes causes low levels of AAT in the serum, resulting in lung tissue damage by proteinases. AAT is the second most abundant protein in the blood. A effective method to treat COPD is to stop AAT forming multiple chains in the liver and allow the protein coming out. Secretion of the protein may simultaneously alleviate both the liver and the lung diseases. Protein structural analysis have identified the site responsible for AAT polymerization (chains). This site is an attractive target for drug design. We think that specific small molecules that interfere with AAT polymerization can be identified by a molecular docking approach and these small molecules can be developed into novel therapeutic drugs. We have used computer-based molecular docking program and the NCI/Developmental Therapeutics Program (NCI/DTP) depository to identify promising compounds that demonstrate efficacy to enhance secretion of AAT protein. We have obtained US patent for these molecules. Our objective is to develop these small molecules into clinical useful drugs. In this proposed study, we will test and validate these compounds in cell and animal models. The preclinical study will be the scientific basis for subsequent clinical trials.

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Doug Cress, Ph.D.	H. Lee Moffitt Cancer Research Center	Proliferative Signatures to Predict the Benefit of Adjuvant Chemotherapy in Early-Stage Non-small Cell Lung Cancer	Stage 1 lung cancer patients have only a 50% chance of surviving for five years. We believe that many of these patients should be treated more aggressively than is currently recommended. Since 2010, these patients are treated surgically and are released, based on evidence that the group as a whole, does not benefit. However, since HALF of them will recur and die we can surmise that many were not cancer free after surgery. These might have benefitted from adjuvant (given after surgery) chemotherapy, but in the past there was no way to tell which patients would benefit. Recognizing this problem, we have identified a genetic signature that may identify early-staged tumors that have deadly potential. We have developed our signature into a relatively simple and inexpensive test based on Nano-String barcode technology. This test can be used on standard pathology sides (even if they are decades old).It would be very expensive to prove that our test works by conducting a clinical trial in which patients would be randomized into two arms. Fortunately, the trial has already been done, in two ways. First, a study was published in 2010 by the Spanish Lung Cancer Group that essentially performed the definitive clinical trial on treatment decisions for early staged lung cancer and they have provided the pathology slides from 223 of those patients. Second, we have utilized our access to samples from Floridian-based patients to identify a cohort of about 399 patients one-third of which were treated with ACT. We will also perform mutational analysis on these cohorts. We will use these two cohorts to further prove that our test works and validate how well it works in combination with other predictors such as mutation analysis.

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Elizabeth A. Shenkman, Ph.D.	University of Florida	OneFlorida Cancer Control Network	The purpose of our project is to reduce tobacco-related health disparities in Florida by enhancing the infrastructure available to conduct tobacco-related cancer and cardiovascular disease (CVD) research. The infrastructure will enable pragmatic clinical trials and implementation studies in real world, primary care settings and will increase physician capacity to follow evidence-based guidelines for tobacco-related risk factor screening and brief interventions. Primary care providers play a critical role in tobacco-related disease screening, counseling, and early intervention. Developing a research infrastructure within primary care settings, particularly among practices serving vulnerable populations, is essential to: (1) expand the inclusion of under-represented groups in tobacco-related disease research; (2) conduct research in care delivery settings to enhance the validity of the research; and (3) facilitate the conduct of studies focused on the implementation of evidence-based practices. The OneFlorida Cancer Control Network (CCN) includes four distinct systems touching all 67 counties and representing over 9 million Floridians: (1) University of Florida Health System; (2) Orlando Health; (3) Health IMPACTS practice-based research network in collaboration with Florida State University; and (4) the University of Miami Health System. In 2012, One Florida CCN cared for 39% of all Floridians, through a network of 22 hospitals, 416 clinic settings, and 3,250 physician providers. Our aims are to: (1) Enhance the infrastructure available to scientists throughout Florida, including those at historically black colleges and universities, to conduct pragmatic clinical trials and implementation science studies in primary care settings for tobacco-related cancer and CVD; (2) Enhance the infrastructure available for tracking study participation, participant accrual, and findings using an online, interactive webportal. (3) Create a Pragmatic Clinical Trials and Implementation Science Minority Education Program. (4) Engage primary care practices in tobacco-related disease research within the OneFlorida CCN by implementing a pilot, pragmatic clinical trial related to evidence-based tobacco cessation strategies.

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Scott Antonia, Ph.D., M.D.	H. Lee Moffitt Cancer Center	Expansion of enduring infrastructure to support lung cancer screening research	The majority of people who are diagnosed with lung cancer will die from their disease due to the late stage at diagnosis. Early stage cancer is curable, and so earlier detection saves lives. For decades a screening test to detect early stage lung cancer has been elusive even among high-risk individuals. However a recent randomized trial (National Lung Screening Trial) demonstrated the efficacy in screening CT scans in terms of lives saved. At the Moffitt Cancer Center we have established a comprehensive clinical lung cancer screening program including a team of radiologists, pulmonologists, thoracic surgeons, and medical oncologists who work together not only to detect lung parenchymal abnormalities but also to properly interpret the findings and devise appropriate courses of action to manage these findings. We now propose to improve and expand this infrastructure to include a team of investigators to address persistent problems and unanswered questions in lung cancer screening. These investigators include epidemiologists, biostatisticians, CT image analysts, behavioral scientists, and smoking cessation experts who will come together to improve the effectiveness of CT screening and increase lives saved. There remain a number of issues which hamper the realization of the potential benefit of lung cancer screening. The implementation and adoption has been slow, with a very small fraction of people who could benefit actually undergoing CT screening. The behavioral scientists on the team will determine perspectives of key individuals who influence the implementation of screening, laying the foundation for future interventions to increase the frequency of screening. Controversy remains regarding true benefit of lung cancer screening. For example, a recent Medicare advisory panel had concerns about low-dose CT screening. Therefore there is need for a comprehensive screening registry that includes participant data, outcomes, clinical data, and quantitative radiological features. These data will allow for additional research on the benefits of CT screening which may refine the current recommendation criteria. A known problem with screening is the discovery of lung parenchymal abnormalities that are false positives. This results in additional, sometimes invasive testing, incurring additional cost, morbidity, and anxiety. We plan to digitally capture the screening CT images and integrate the image features along with outcome analyses which could better predict false positives and reduce additional testing for some individuals. Finally we propose that the emotional response to CT findings, whether positive or negative, creates a teachable moment that has the potential to increase smoking cessation, reducing the risk of developing lung cancer in the screened individuals. Our team includes experts in the psychology of smoking cessation, and we will test methods in this setting. Our research findings will be immediately exportable to the other academic health centers and community hospitals throughout the state which will have an impact on reducing the incidence late stage, incurable lung cancer in Florida.