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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Derek C. Radisky, Ph.D.	Mayo Clinic	Development of Assays for Individualized Breast Cancer Risk Prediction	More than 1 million women in the US every year undergo breast biopsies for mammographic abnormalities or palpable lesions. The majority of these women have nonmalignant breast lesions that are classified as benign breast disease (BBD). Because they have BBD, these women are known to have significantly elevated risk of progression to breast cancer, but at present there is little information that a woman with BBD can use to determine her individual risk. Two key clinical questions arise from these observations. Can we identify which of these women are most likely to develop breast cancer? If we can identify high risk patients, then what can we do to reduce cancer mortality among them? The first part of our proposal focuses on identification of women who are at risk for developing estrogen receptorpositive breast cancer and who thus would benefit from chemo preventive endocrine therapy. A parallel aim is to identify women who are at risk of developing aggressive breast cancers for which current treatment methods are not as effective, and for which more frequent mammography could be recommended to identify disease at the earliest possible stage. We propose to develop a rapid and inexpensive clinical assay that uses RNA from benign breast biopsies to assess molecular markers as the basis for an individualized model for breast cancer risk prediction. A robust breast cancer risk model would help focus chemoprevention and surveillance efforts towards those women who would benefit most from them, and could also identify women who are at low risk, reducing unnecessary patient anxiety and helping providers to establish an appropriately informed schedule for future surveillance. Successful completion of our aims thus will be "practice changing" and will decrease both the incidence of and the mortality associated with breast cancer among women who have been diagnosed with BBD.

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Minjung Kim, Ph.D.	H. Lee Moffitt Cancer Center	Elucidating the Role of R-Ras Activation in Melanoma Tumorigenesis	Melanoma is the deadliest form of the skin cancers. Abnormally activated Ras proteins have been reported to contribute for melanoma formation. Ras family includes many closely related different forms of Ras proteins such as H-, K-, N-, R-, and M-Ras. Among them, mutations that activate N-Ras has been observed in 15~20% of melanoma patients. Recently, we and others made an observation that melanoma often inactivates negative regulator of Ras proteins, called RasGAPs, to activate Ras. In particular, we have shown that RASA1, one of the RasGAPs, is inactivated in melanoma by inactivating mutations or by loss of protein, suppresses melanoma growth by inhibiting R-Ras protein, and confers decreased response to BRAF targeted therapy. We also observed that melanoma patients with activating BRAF mutations (the most common mutations occurring in 40~60% of melanoma patients) survived longer when they express RASA1 at high level. The objective of this proposed study is to study whether and how R-Ras is activated in melanoma patients, whether R-Ras activation can enhance growth of melanoma cells with BRAF activation, and whether R-Ras can be targeted to treat melanoma in mice. In this end, we will identify RasGAPs, of which inactivation leads to R-Ras activation and desensitization to BRAF targeted therapy, will address whether R-Ras activation enhances formation, growth, and spread of melanomas with BRAF mutation, and will test whether R-Ras inhibition can lead to tumor shrinkage in mice. We will also generate a mouse model with loss of RASA1 and activation of BRAF. Therefore, this proposed study will establish the importance of R-Ras activation for melanoma formation and its inhibition for treatment.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Jennifer J. Hu, Ph.D.	University of Miami	Impact of Etiology-Driven Precision Medicine on Reducing Breast Cancer Disparities	Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer death in American women; underserved minorities remain at a higher risk of dying from breast cancer in part due to a higher prevalence of a more aggressive breast cancer type, triple negative breast cancer (TNBC). Recent discoveries in genomics have improved breast cancer risk prediction and survival. However, translating this knowledge to precision medicine has not been possible due to the lack of prediction models of etiology and treatment response. Therefore, we will bridge this critical scientific knowledge gap by developing novel prediction models of aggressive breast cancer, particularly TNBC. We will test the working hypothesis that genetic variations, dietary factors, metabolite profiles, and tumor changes are associated with more aggressive TNBC and worse survival. We will build a paradigm-shift model system to translate etiology to precision medicine. It is anticipated that this model system will have high impact on breast cancer research and precision medicine. We will study gene-gene and genediet interactions in TNBC risk, metabolite signatures of TNBC, and tumor changes. Capitalizing on a large underserved minority breast cancer patient population, promising pilot data, strong institutional commitment, and multi-disciplinary research team, we are in an exceptional position to conduct the proposed research. In summary, we aim to bridge a critical scientific knowledge gap in translating genomic/metabolite profiles to transform breast cancer research and precision medicine to ensure that every breast cancer patient receives treatment(s) with the optimal efficacy and minimal side effects, particularly in underserved minorities with higher prevalence of TNBC and worse survival.

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Eric Haura, M.D.	H. Lee Moffitt Cancer Center	Signalingassociated Protein Complexes for the Molecular Annotation of Therapeutic Vulnerabilities, Resistanceassociated Signaling & Tumor Heterogeneity in Lung Cancer	This research will study ways to identify and overcome drug resistance in lung cancer. In recent years, it has become standard of care to identify altered genes in lung cancer patients as identification of these genes can predict response to pill based therapy. However, resistance to treatment is universal, and this precludes the cure of patients with advanced lung cancer. One major driver of resistance is the activation of other proteins that bypass the utility of the pill based therapy. This can occur through new changes in the tumor cell or can be drive by noncancer cells in the tumor. Importantly, genes, encoded by DNA, do not function in isolation but rather as part of larger molecular machines. Our research is focusing on the importance of these machines in affecting drug resistance. We will use new technology to identify and create systems to read out these machines in cancer tissues from patients. This project will expand our research capacity in Florida and will improve the treatment of patients with lung cancer. The work can ultimately enhance enrollment on clinical trials by developing new tools to optimize treatment decisions for patients and their physicians.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Ranjan J. Perera, Ph.D.	Sanford-Burnham Medical Research Institution	The Expansion and Upgrade of the Analytical Genomics Core Infrastructure at Sanford-Burnham Medical Research Institute	The current application proposes to create a central advanced genomics facility by upgrading and expanding the existing Analytical Genomics Core at the Sanford-Burnham Medical Research Institute at Lake Nona (SBMRI). Although the potential for genomic medicine to contribute to patient care has long been recognized, translating laboratory discoveries to the clinic has been a relatively slow process. At present, much of this work is performed by teams working in isolation, and more structured collaborations and sharing of advanced genomics and bioinformatics data will greatly enhance future cancer genomic research as well as clinical translational efforts in the state of Florida. The Analytical Genomics Core facility at SBMRI houses powerful technology platforms for advanced genomics research, including nextgeneration DNA sequencing capabilities, with core competencies in bioinformatics and biostatistics. Together, these facilities have empowered researchers in Florida to make seminal contributions to translational cancer research, such as the discovery and development of therapeutics and biomarkers. The Analytical Genomics Core team is already working closely with leading researchers in major cancer centers in the state (Moffitt Cancer Center, Florida Hospital Cancer Institute, University of Florida College of Medicine and Shands Cancer Center, University of Miami Miller School of Medicine, Sylvester Comprehensive Cancer Center/Braman Family Breast Cancer Institute, University of Central Florida, and Florida International University). The existing SBMRI Analytical Genomics facility is currently running at 80% of capacity. If funded, this application to upgrade and expand the facility's infrastructure will further boost this capacity and enable researchers at Florida cancer centers to conduct first-class translational cancer research by providing access to advanced genomics and bioinformatics platforms.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Anthony Capobianco, Ph.D.	University of Miami	Lead Optimization and Preclinical Evaluation of Small Molecule Inhibitors of Notch Transcriptional Activation	In many human cancers, deregulation of the Notch pathway has been shown to play a role in tumorigenesis. Aberrant Notch activity also plays a central role in the maintenance and survival of cancer stem cells, which may underlie a role in metastasis and resistance to therapy. Since Notch plays an important and diverse role in cancer, it has become an exceedingly attractive target for cancer therapeutics. However, the full range of potential targets in the pathway have been under-explored. To date, there are no small molecule inhibitors that directly target the intracellular Notch pathway. Notch mediates the formation of a core transcriptional activation complex, termed the Notch Ternary Complex (NTC), thus initiating and maintaining a transcriptional cascade. The NTC comprises the DNA binding protein CSL, the intracellular domain of Notch (NICD) and the co-activator protein Mastermind (Maml1). The overarching hypothesis of this proposal is that compounds that prevent the recruitment of Maml1 by targeting NICD would be potent inhibitors of the Notch pathway. We have identified a lead compound (1- 134-83) that is a bona fide inhibitor of the NTC that uncouples the Notch-mediated transcriptional cascade and inhibits tumor growth in patient derived mouse models of cancer. Therefore, the overall goal of this project is to optimize the scaffold of the lead compound (1-134-83) to identify clinical candidates that inhibit NTC assembly in order to develop novel potent drug-like small molecule inhibitors of Notch-mediated transcription. To this end, we will use an innovative approach that combines current state-of-the-art computational, biochemical and biophysical techniques. Successful completion of this study will fulfill an unmet need in terms of therapeutic agents targeting the Notch signaling pathway, providing specific inhibition of the Notch transcriptional activation complex, which could complement and/or offer an alternative to current therapeutic approaches. We will achieve the goals of this proposal through the following specific aims: (I) Lead optimization through structure-activity relationship studies and scaffold hopping, (II) Biochemical and biological assessment of lead analogs, (III) Preclinical evaluation of efficacy of lead clinical candidates. Our recent identification and validation of a small molecule inhibitor of the NTC (1-134-83) demonstrates proof of concept for the proposed research.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Daiqing Liao, Ph.D.	University of Florida	Target HDAC2 for Treating ER-Positive and DrugResistant Breast Cancer	Approximately 75% of breast cancer (BC) is estrogen receptor (ER)-positive (ER+), and the majority of BC deaths occur in women with ER+ breast cancer. This is a quite shocking statistic given the fact that endocrine therapies (e.g., tamoxifen, letrozole and fulvestrant) that effectively block ER function in BC are widely used and have significantly prolonged the survival for many women with ER+ breast cancer. However, although ER positivity in breast tumors is generally a reliable predictor for treatment response to endocrine therapies, about 50% of ER+ breast cancer fails to respond to such therapies, and ER+ but endocrine therapy-resistant BC generally has poor prognosis. According to current estimate, approximately 90,000 new cases of ER+ BC in the United States alone would not respond to endocrine therapies. Therefore, a critically important objective in the breast cancer community is (1) to determine the key factors for treatment failure, (2) to identify new therapeutic targets and (3) to develop new therapies that overcome drug resistance and effectively kill cancer cells. Through analyzing data from thousands of BC patients, increased production of HDAC2 in cancer was found to correlate with resistance to endocrine therapies and shortened survival for patients with ER+ breast cancer. HDAC2 is an enzyme that probably assists ER to promote cancer cell proliferation. Importantly, HDAC2 is a "druggable" target. Thus, drugs that stop HDAC2 can be developed for treating ER+ and drug-resistant BC. In this project, drug leads that specifically target HDAC2 have been discovered. Our specific goal is to test our novel HDAC2 inhibitors for their effectiveness in suppressing the growth of ER+ breast tumors as well as their metastasis to other organs using breast cancer animal models that closely mimic the ER+ cancer in humans. The new HDAC2 inhibitors are small-molecule compounds and are thus suitable for various systemic treatments, such as via oral administration. Because the new agents are highly selective to inhibit HDAC2, they are less likely to hit other targets in the human body, and thus are expected to be safer than less selective drugs that target numerous HDACs. This project may lead to a drug candidate specifically targeting HDAC2 with a desirable safety profile and drug properties that are suitable for clinical trials in patients with ER+ and endocrine therapy-resistant breast cancer. This project, if successful, is expected to provide a new and effective therapy to increase the survival of a significant population of women with ER+ BC that do not respond to currently available endocrine therapies.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
David D. Tran, M.D., Ph.D.	University of Florida	Novel Strategies to Target Disseminated Tumor Cells in Triple Negative Breast Cancer	Patients with locally advanced triple negative breast cancer (TNBC) who have persistent disease after chemoradiation are at a significantly increased risk of developing lethal metastasis within two years after diagnosis. Currently no known therapy can prevent this development. A major cause of this high metastatic risk is the presence of cancer cells residing in distant organs after having spread there from the primary tumor well before the tumor is treated and surgically removed. Some of these metastatic cells, known as disseminated tumor cells (DTC), are thought to represent cancer stem cells that are dividing slowly and therefore highly resistant to treatment. These low-proliferative DTCs (lpDTCs) can persist in distant organs for an extended period of time before becoming reactivated to form metastasis. Attempts at eliminating lpDTCs have not been successful due to a poor understanding of their biology and a lack of therapeutic targets. To this end, we recently identified a critical signaling pathway present in lpDTCs that is responsible for their quiescence and treatment resistance. This pathway consists of a circular signaling loop involving the p38MAPK and TWIST1 proteins, both of which have been found to regulate breast cancer metastasis. In cultured breast cancer cells and mouse models of breast cancer, we demonstrated that lpDTCs could be forced out of quiescence simply by inhibiting their p38 pathway. More importantly, once reactivated, lpDTCs became exquisitely sensitive to chemotherapy, indicating that p38 is attractive therapeutic target. In this proposal, we will test the innovative therapeutic concept that lpDTCs in TNBC can be eradicated when they are induced to divide again while being exposed to chemotherapy. We shall achieve this goal by using PH797804, a highly selective, potent, well-tolerated p38 inhibitor, to reactivate lpDTCs, followed by treatment with carboplatin chemotherapy in patients with TNBC who have persistent disease and lpDTCs after chemoradiation. First we will establish that the combination is safe and effective at reactivating lpDTCs, initially using mouse models of aggressive breast cancer, then followed by a phase I trial enrolling patients who have advanced metastatic breast cancer. The goal of the phase 1 study is to determine the maximal tolerated dose (MTD) of PH797804 plus carboplatin that is effective at reactivating lpDTCs. The MTD will be used for a phase 2 study testing whether the combination of PH797804 plus carboplatin results in improved progression-free survival at 2 years and eventually lead to better overall survival. If successful, this innovative therapeutic concept has the potential to change clinical practice not only in aggressive breast cancer but also in many other aggressive cancers.In the last and equally exciting aim, we will perform comprehensive genomic analysis of samples collected at different stages of metastasis and couple it with ARACNe, a powerful computational platform, to identify genetic driver mutations and changes in signaling pathways relevant to transitions between these stages. The goals are to 1) provide further insights into the mechanism of how lpDTCs are generated and maintained; and 2) yield additional therapeutic targets to eliminate lpDTCs and improve this novel treatment approach.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Aubrey Thompson, Ph.D.	Mayo Clinic Florida	Predictive Markers of HER2-Targeted Therapy	The use of humanized monoclonal antibodies such as trastuzumab (Herceptin®) has dramatically improved outcome in breast cancer patients who overexpress the HER2 receptor (HER2+ tumors). Treatment of early stage HER+ tumors with trastuzumab results in long term diseasefree survival in ~75% in patients with HER2+ breast cancer. However, 25% of patients with early stage HER2+ disease relapse after trastuzumab. The prognosis for patients who relapse is much worse. This is a very important point: patients who respond to first line therapy are effectively cured; whereas patients who relapse after first line therapy are at grave risk. The clinical challenge is to identify the patients who are at high risk of relapse after first line therapy with trastuzumab. We have recently completed genomic analysis of patients from a very large clinical trial of early stage HER2+ tumors treated with trastuzumab (NCCTG/Alliance N9831, Edith Perez, principal investigator). We used these genomic data to identify a set of immune function genes that are linked to favorable outcome, and we built a "first draft" model that predicts outcome in early stage HER2+ tumors treated with trastuzumab. This model identified a cohort of patients who were depleted of immune function genes and who derived little or no benefit from trastuzumab. The ability to predict response to trastuzumab has great clinical significance. Patients who are unlikely to benefit can be spared the expense (~$40K) of trastuzumab, as well as the risk of adverse heart events associated with this therapy. Patients who are more likely to relapse can be evaluated as candidates for some of the newer, and even more costly, anti-HER2 therapies that are currently being approved or are being tested in clinical trials. Third, these are likely to be the patients who should be enrolled in clinical trials to test newly emerging therapies to activate the patient's immune system against the tumor. Our predictive model therefore has great potential for rapid translation into clinical medicine, and we have been approached by several companies (Nanostring, Agendia, Illumina) who are interested in licensing this assay. However, before the assay can be licensed, several key steps are necessary. We must carry out analytical validation of the assay using a platform that is adaptable to routine clinical analysis. Once that has been accomplished, we must demonstrate clinical validity using an independent sample cohort to show that our model works for patients other than those used to develop the model. Once these parameters have been locked down, commercialization of the assay is essentially assured. These objectives therefore define the aims of this technology validation and transfer proposal.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Michael Antoni, Ph.D.	University of Miami	Stress Management Effects on Affective Status and Influenza Vaccine Response in Older Breast Cancer Patients	Women undergoing breast cancer (BCa) treatment face many stressors and experience increased negative affective/mood states (depressed mood, anxiety) and decreased positive affect (happiness, contentment). These not only compromise their quality of life but, as we have shown, also contribute to inflammation and negative health effects, including on their immune system. This application brings together our research and intervention strengths for psychosocial intervention and the aging immune system for BCa patients. It is well established that systemic inflammation increases with aging, negative affect and cancer treatment and our hypothesis is that older women (60yrs+) who confront the challenges of BCa treatment have less coping resources than younger women, resulting in greater negative affect and depressive symptoms. The proposed studies will address these issues and contribute to the health, well- being, and longevity of BCa patients. Our studies identified immune and psychological biomarkers for optimal humoral immune response in older humans as measured by the antibody response to the influenza vaccine and decreased inflammation. We found poorer Affective Status (greater negative and less positive affect) is associated with lower immune response. Little is known about the impact of Affective status and inflammation on IR in particularly vulnerable older populations, such as women undergoing BCa treatment. Our prior studies have shown 1) poorer Affective status (depression) associates with greater levels of inflammatory cytokines in the weeks after BCa surgery, 2) behavioral intervention (cognitive behavioral stress management (CBSM)) improves Affective Status (decreases negative affect and depressive symptoms and increases positive affect), and 3) CBSM also reduces leukocyte pro-inflammatory gene expression during BCa treatment and also in older BCa patients in particular. Our hypothesis is that CBSM will decrease negative affect and inflammation and improve immune response, in the target sample of older BCa patients who report elevated levels of distress. We propose to recruit older BCa patients (60yrs +) with elevated distress levels up to 8 weeks after surgery, measure Immune Status (inflammation and immune function) and Affective Status as well as other potential confounders. They will then be randomly assigned to either 10 weeks of Remotely Delivered (via tablet with broadband connection) group-based CBSM commencing just after T0, or a WaitList control (WLC) condition that will receive an identical 10 week Remotely Delivered group-based CBSM after study completion. Similar measures will be done and at 6 month follow-up and 7 days and 28 days after the seasonal influenza vaccine (IV). We will examine intervention group differences in the serum response to IV at as the primary outcome. We will also test the effects of CBSM on changes in affective status, inflammatory measures (e.g., serum cytokines), and immune measures and associate these with the changes in serum response to IV. This innovative approach will 1) use remote technology, designed to reach a wide range of patients, to 2) improve the overall immune response in older women with BCa, both supporting a strong public health significance. This approach would support future delivery of psychosocial interventions during treatment for other cancers in underserved groups.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Michael P. Kladde, Ph.D.	University of Florida	Temporal Epigenetic Mechanisms in Breast Cancer Oncogenesis	The permanent inactivation of critical genes that protect cells against cancers, termed tumor suppressor genes (TSGs), is a well-established event in cancer progression. TSG inactivation is often caused by changes or mutations in the sequence of the A, C, G, and T bases or rungs on the ladder that make up the DNA double helix, destroying the function of the protein specified by a TSG. Recent scientific advances have also recognized that TSGs in tumors frequently have normal, non-mutated DNA sequences, although the TSG is not expressed to produce protein as it is inactivated by alterations in molecular characteristics that regulate gene expression, referred to as epigenetic regulation. Much has been learned about this mode of regulation with regard to the types and gross placement of epigenetic changes that occur in cancer cell DNA compared with normal cells; however, we have a limited understanding about the order and precise location of the initial or primary epigenetic alterations in TSGs that drive their silencing in cancer. Based on our preliminary findings, we hypothesize that DNA sequences that promote expression of TSGs become more tightly packed in particles called nucleosomes, and this increased packaging precedes the accumulation of repressive chemical changes in DNA, i.e., DNA methylation, which reinforces an aberrant epigenetic environment that silences TSG expression. To test this hypothesis, we will use a progression model of breast cancer formation; specifically, introducing a copy of an oncogene (Ha-ras) into non-cancerous human mammary epithelial cells (HMEC) to drive oncogenic transformation and new (de novo) epigenetic silencing. Using this approach, we will then monitor the temporal sequence of molecular events that accompany silencing of select loci with pinpoint accuracy. These studies will employ innovative, integrative single-molecule assays that we have developed to directly relate changes in the presence and positions of nucleosomes and DNA methylation on TSG promoter sequences to gene expression, i.e., synthesis of RNA transcripts that encode for TSG proteins. Elucidating epigenetic mechanisms driving cellular transformation is crucial to a better understanding of cancer etiology and will aid the identification of early diagnostic markers and novel targets for therapeutic intervention.

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Nupam Mahajan, Ph.D.	H. Lee Moffitt Cancer Center & Research Institute	Epigenetic Regulation of Androgen Receptor in Castration Resistant Prostate Cancer	For over half a century, prostate cancer research has focused on the protein expressed in male reproductive system including in prostate, Androgen receptor (AR). AR binds to androgen or testosterone and gets activated to perform its function as transcriptional co-activator. However, cancer cells hijack AR's transcriptional activity and thus in cancer cells, AR is not only necessary for initiation and growth of the disease, but also plays a crucial role in its progression to the highly metastatic stage, commonly referred to as castration resistant prostate cancer or CRPC. Due to absolute dependence on AR, anti-androgens were common therapeutic modality for patient with this disease, wherein AR was deprived of its biological ligand, androgen. This resulted in loss of AR transcriptional activity leading to suppression of tumor growth. Although effective initially, antiandrogen therapies soon lost its effectiveness; these patients rapidly developed drug-resistance and progressed to CRPC stage. Interestingly, CRPC tumors maintained high AR levels even when prostate cancer cells were exposed to protracted androgen-deprivation therapy. Presence of elevated AR levels in spite of prolonged AR antagonist treatment in CRPCs is a paradox that has mystified researchers. Over the years this has emerged to be the topic of intensive research due to obvious therapeutic benefits that could be drawn if understanding of the mechanism were to be obtained. We uncovered a novel mechanism of auto-regulation of AR transcription wherein AR protein coordinated functionally with another protein called ACK1. AR when complexed with ACK1 performed a new task- they facilitated modification of a DNA binding protein called histone H4. Significantly, they not only modified the histone, but also deposited these abundant proteins specifically near AR gene, causing AR expression even when androgen was absent. Significantly, these data have exposed an Achilles' heel for targeting new treatment strategies in CRPCs-disruption of ACK1/AR interaction could sensitize CRPC tumors. To achieve therapeutic benefit from this new signaling event, we generated a novel ACK1 small molecule inhibitor (R)- 9bMS, which not only inhibited ACK1 activity and AR expression but also suppressed CRPC tumor growth in mice. Overall, our preliminary data indicates that disruption of ACK1-AR interaction by novel ACK1 inhibitor (R)-9bMS opens up a new therapeutic option for this essentially incurable malignancy. In this proposal will perform detailed mechanistic & in vivo studies to test efficacy of (R)-9bMS as a new class of prostate cancer inhibitor. Successful completion of this proposal could lead to availability of a potent inhibitor of metastatic prostate cancer, a desperate need for aging American male population.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Walter O'Dell, Ph.D.	University of Florida	Early Markers of Subclinical Pulmonary Vascular Radiation Toxicity in Breast Cancer	Over 200,000 women each year are diagnosed with breast cancer. With improved early detection and treatment more breast cancer patients experience long-term survival. There are over 2.8 million breast cancer survivors in the US and Florida alone contributes roughly 9,000 additions breast cancer survivors annually. Most patients are treated with radiation therapy (RT) to the affected breast and chest wall to minimize the risk for recurrence. However, the lung is highly susceptible to radiation and even with our best methods for minimizing exposure of the lung, 14% of breast cancer patients treated with radiation develop clinical lung toxicity (evidenced by pain and/or reduced breathing capacity), with 4% overall experiencing high-grade clinical toxicity. The use of protons rather than X-rays for radiation treatment holds tremendous promise for reducing exposure of the lung during breast RT, but until now it has been difficult to quantify its actual benefit in human subjects. Our team has recently developed and demonstrated tools to characterize radiation-induced vascular injury in the lungs of cancer patients using only conventional 3D X-ray computed tomography (CT) chest images. In the first part of this project we will take repeat CT scans in patients receiving conventional radiation or proton therapy to study the development and extent of lung vessel damage following treatment and compare the two treatment approaches. Our goal is to provide direct evidence to support/refute the predictions that using protons for treatment will reduce the amount of damage to the lung. In the second part of this study, we will look at a select group of proteins that are released into the bloodstream to try to better understand which of these contribute to the long-term damage in the lung and other organs. This task builds upon many years of experience our team has in studying radiation in animal models. In part 3, we will use our mathematical modeling skills to tie the newly found data from parts 1 and 2 to existing models of how lung tissue responds to radiation. We will use the new data to extend our scientific models to give us a better understanding of the factors that cause radiation toxicity. With these improved models, we will then be better able to identify which patients will experience high-grade clinical toxicity before they undergo treatment so that we can change the method of treatment or make available to them medications that can protect normal tissue from the radiation. Together, the vessel analysis and modeling tools will help in the future to test whether new medications or treatment approaches are effective and safe

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Anthony Capobianco, Ph.D.	University of Miami	Development of Small Molecule Inhibitors of NACK as Novel Cancer Therapeutic Agents Targeting the Notch Pathway	Aberrant Notch signaling is linked to many human cancers. Notch signaling has been demonstrated to play a vital role in the initiation and maintenance of the neoplastic phenotype as well as in cancer stem cell selfrenewal, which may underlie a role in metastasis and resistance to chemotherapy. In this regard, Notch has become an exceedingly attractive therapeutic target in cancer. However, full range of potential inhibitors targeting the pathway has not been well explored. Notch signaling mediates its effects by forming a core transcriptional scaffold, termed as the Notch Ternary Complex (NTC), which is comprised of Notch intracellular domain (NICD), Mastermind (Maml) and DNA binding protein CSL. There is a great interest in designing small molecule inhibitors to directly target the Notch transcription complex, either by blocking the assembly of Notch transcriptional activation complex or by inhibiting the activation of the Notch pathway. Previously, we reported the identification and characterization of NACK, which acts as a Notch transcriptional co-activator and an essential regulator of Notch-mediated tumorigenesis and development. Furthermore, NACK functions in an ATP dependent manner to bind to the Notch transcription complex and to activate Notch-mediated transcription. Given the critical role of NACK in Notch pathway, we hypothesize small molecule inhibitors of NACK activity will function as specific Notch transcriptional activity inhibitors, and therefore be effective as anti-neoplastic agents for Notch-dependent tumors. We have identified a lead inhibitor of NACK (iNACK, Z271-0326), a bona fide inhibitor of NACK, which can interrupt NACK recruitment to the Notch transcription complex that inhibits Notchmediated transcriptional cascade and suppresses tumor growth in patient derived xenograft (PDX) cancer mouse models. The overall goal of this project is to develop and validate additional lead candidates from the scaffold of the lead compound (iNACK, Z271-0326) to develop novel potent drug-like small molecule inhibitors of NACK as clinical candidates. Our current discovery of iNACK (Z271-0326) demonstrated the proof of concept for the proposed research. We will use a sophisticated approach, which combines the cutting-edge computational, biochemical and biophysical techniques, to discover small molecule inhibitors of NACK targeting the Notch transcription complex. Successful completion of this proposal will provide specific and direct inhibition of the Notch transcriptional activation complex, which will open avenues for the development of new therapies for the Notch-dependent cancers. We will achieve this goal through the following three specific aims: (1) Lead optimization of NACK inhibitor Z271-0326 by iterative computational design and chemical synthesis of the predicted best compounds, (2) Identification and validation of lead analogs of iNACK through biochemical and biological assessment, (3) Preclinical evaluation of lead clinical candidates.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Andrew Judge, Ph.D.	University of Florida	Initiating Mechanisms of Cancer Cachexia	Cachexia is a devastating condition that affects up to 80% of cancer patients and is characterized and defined by progressive skeletal muscle wasting and body weight loss. This loss of muscle mass contributes to significant muscle weakness and diminished physical function and quality of life, and is associated with reduced tolerance to chemotherapy and increased complications from surgical and radiotherapeutic treatments. Consequently, cachexia decreases survival time in cancer patients and cachexia itself is estimated to be responsible for up to 30% of all cancer related deaths. However, unfortunately there are currently no medical therapies to counter cancerinduced muscle wasting which is due, in part, to a lack of understanding of the initiating mechanisms. This proposal was developed to identify novel mechanisms which initiate limb and respiratory muscle wasting in response to cancers of the lung, colon and pancreas, which is critical to the development of therapeutic strategies to enhance the quality of life and survival of cancer patients. Specifically our proposal will focus on the role that two specific proteins, called interleukin 8 and CXCL1, play in the initiation of cancer-induced muscle wasting. Both of these proteins are increased in the serum of cancer patients and their receptors are increased in the muscle of cancer patients. We will therefore study the biological importance of these proteins and their receptors as they relate to cancer cachexia.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Emmanuel Thomas, M.D., Ph.D.	University of Miami	Identifying Infection and Molecular Determinants of Health Disparities in HCV Infected Minority Populations for the Prevention and Early Detection of HCC	HCV infection is the most common blood-borne infection in the U.S. with estimates of 4 million HCV-infected individuals in the U.S. and 170 million worldwide. About 30% of individuals with persistent infection develop chronic liver disease including cirrhosis and hepatocellular carcinoma (HCC). HCC is directly linked to obesity and it is one of the few cancers whose frequency is increasing in the U.S. mainly due to the aging HCV infected population. Given the increasing incidence of obesity throughout the U.S., HCC will become increasingly important unless current trends are dampened through intervention. In South Florida, where the incidence of HCV infection is highest among minority populations, the endemic high prevalence predisposes this population to the development of HCC. This cancer is frequently diagnosed in the later stages and it has a median survival of 6-20 months, resulting in 250,000-1,000,000 deaths/year. Major gaps exist in our understanding of the progression from HCV infection to severe clinical outcomes such as the development of HCC. In addition, HCV infection is more prevalent among African Americans than among persons of any other racial group in the United States. Furthermore, patients of European ancestry have a significantly higher probability of spontaneously clearing the virus than patients of African ancestry. Fortunately, very potent antiviral agents, utilizing shortened treatment durations, are now FDA approved. Consequently, a unique opportunity now exists to minimize health disparities resulting from this virus infection. However, it is significant that if a patient has evidence of liver disease, they are still at risk for the development of liver cancer/HCC even after cure of HCV. Our research aims to prevent HCC and promote screening and early identification through efforts to monitor patients at increased risk. We will identify those most susceptible to poor clinical outcomes including the development of liver cancer. Because HCV is the leading cause of liver cancer, these efforts may prevent the development of hepatic tumors that would otherwise arise over the next decade.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Clement K. Gwede, Ph.D., M.P.H., R.N.	Moffitt Cancer Center and Research Institute	Community CARES: A Multilevel Intervention to Increase Colorectal Cancer Screening Adherence in Community Clinics	A leading cause of death in the U.S. is colorectal cancer (CRC). It is a significant health concern that affects both men and women and one that our local community has identified as important. Many adults do not get screened for colorectal cancer for reasons such as limited access to screening tests, information that is difficult to understand, as well as other sociocultural and environmental factors. Community involvement is needed for sustainable solutions. The proposed study called Community CARES (Colorectal Cancer Awareness, Research, Education and Screening) or C-CARES for short, tests a promising intervention delivered in Federally Qualified Health Centers (FQHCs). It builds on the work of a well-established community partnership network (the Tampa Bay Community Cancer Network), that was formed over a decade ago to address health disparities through education, outreach and research. C-CARES is also fueled by a new generation of high sensitivity and high specificity fecal immunochemical test (FIT) that can be widely delivered at a lower cost (compared with colonoscopy), and done conveniently in the privacy of one's home. We recently completed an intervention study in clinics called CARES that was guided by community members, and which tested low-literacy materials (i.e., photonovella+DVD) + FIT. In this study, 80% of participants got screened with FIT, a rate that exceeds Healthy People 2020 CRC screening goal of 70.5% and the national goal to reach 80% by 2018. Although highly beneficial, the CARES study emphasized initial vs. repeat annual screening behaviors to help increase effectiveness of FIT. The study also did not provide follow-up intervention on 20% of patients who did not respond to the initial intervention. C-CARES extends this foundational work by collaborating with community clinics. It seeks to implement a multicomponent, dual-language (English/Spanish), theory-driven educational intervention to promote long-term annual FIT. In Phase I - the Preparatory Phase (months 0-6), the team activates its Community Advisory Board, completes packaging of additional C-CARES components, and finalizes procedures to utilize existing electronic medical record systems at the FQHCs—an important tool for identifying eligible patients for screening, delivering patient reminders, and documenting CRC screening completion. In Phase II - the Intervention Phase (months 7-60), a two-arm randomized comparative design will be used to examine whether C-CARES Plus versus C-CARES improves annual FIT screening among 328 individuals, 50-75 years of age, who are not up to date with CRC screening. In the C-CARES group, participants are given CARES materials + FIT kit. In the C-CARES Plus group, a stepped approach is used: participants are given CARES materials + FIT kit plus added personalized components that include one-on-one education, mailed or text message reminders, and booster education and/or coach. We think that C-CARES Plus will result in greater screening rates at 3, 15, and 27 months. This sets the stage for future statewide dissemination for improved community health. The study will also help to impact health disparities in colorectal cancer.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Keiran Smalley, PhD	Moffitt Cancer Center and Research Institute	Defining and Targeting Epigenetic Deregulation in Uveal Melanoma	Uveal melanoma is the most common primary cancer of the eye. It arises from melanocytes that reside in the uveal tract of the eye and tends to be most common in individuals who are at risk for skin melanoma (e.g. blue eyes, blonde hair). Although most patients with uveal melanoma present with local disease only, half will eventually succumb to distant metastases – even when the primary tumor is treated successfully. At this time there are no effective treatments for disseminated uveal melanoma, and even treatments that have proven effective for skin melanoma such as immunotherapy seem ineffective in uveal melanoma. Work from our team has shown that uveal melanomas present as having either a high risk or a low risk of metastasis and that this risk can be determined on the basis of gene expression. We have further observed that it is possible to convert the high risk subset of tumors to low risk through use of drugs that regulate tumor cell plasticity called HDAC (histone deacetylase) inhibitors. We have also found that specific HDAC inhibitors can sensitize uveal melanoma cells to other experimental drugs that are being evaluated in the clinic, such as MEK inhibitors. The goal of this proposal is to determine the mechanisms that push some uveal melanomas into the high risk category and to characterize whether this presents new therapeutic opportunities. Ultimately we wish to design new therapies that target high risk uveal melanoma with the expectation of evaluating these clinically in the near future. This proposal represents a true collaborative effort between three investigators with extensive, complimentary expertise in uveal melanoma (Dr. Harbour), melanoma signaling and therapy (Dr. Smalley) and the mechanisms of tumor cell plasticity (Dr. Licht).

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Amy E. Wright, PhD	Florida Atlantic University	Discovery of Marine Natural Product Antagonists of Survivin as Novel Cancer Therapeutics	The HBOI marine natural products chemical library represents a diverse library of genetically encoded small molecules that have actively co-evolved with cellular targets involved in both cell survival and death. The nodal protein survivin has been identified as an important target for intervention in a number of cancers including colon, lung and breast cancers. It plays key roles in many cancer supporting processes including: inhibiting apoptosis; supporting mitosis and metastasis; conveying drug and radiation resistance through changes in the DNA repair response; inducing angiogenesis, and maintaining stem cell populations. Survivin has been demonstrated to play a role in the aggressiveness of many cancers and its expression correlates to poor prognosis. A number of approaches to antagonize survivin's multiple functions have been explored including vaccination, use of single amino acid mutants, ribozymes, siRNA and small molecule inhibition. Even with these successes, many have significant clinical drawbacks and there remains a need for additional small molecules that antagonize the activity of survivin. We hypothesize that screening the HBOI library for compounds that reduce the levels of surviving will identify novel inhibitors with the potential to be useful as new treatments for cancer or as tool molecules to address the remaining questions in survivin biology. We will specifically focus on discovery of natural products that reduce the levels of activated survivin in colon, lung and breast cancer cell lines bearing activating Ras mutations, where survivin function is especially important. We will use high content imaging (HCI) to rapidly screen chemically diverse materials from the library for their ability to reduce levels of survivin in cancer cell lines. Active compounds will be further profiled for their effects on survivin related processes. Discovery of additional small molecule antagonists will advance this field in both our understanding of basic biology of surviving and in clinical practice.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Xin-Hai Pei, M.D., Ph.D.	University of Miami	Targeting BRCA1 Deficient Breast Cancers	Basal-like breast cancers (BLBCs) are the most lethal breast cancers, partly due to their enrichment with cancer stem cells (CSCs) thought to drive relapse and metastasis. More than one third of BLBCs have dysfunctional BRCA1. Although the majority of BRCA1 deficient cancer patients respond to DNAdamaging agents, tumor recurrence and resistance combine to decrease the survival of such patients. Thus, additional therapies targeting the pathways aberrantly activated by Brca1 deficiency are urgently needed. PKC and CDK6 are major kinases activated in CSCs and BLBCs. Activation of PDGFR signaling results in the PKC-dependent activation of FRA1, thereby leading to the assembly of FRA1- c-JUN complex, activation of epithelial-mesenchymal transition (EMT) program, and generation of CSCs. We discovered that deletion of p16Ink4a (p16) or p18Ink4c (p18), inhibitors of CDK4 and CDK6, in mice led to mammary cell proliferation. Disrupting Brca1 in p16- or p18-deficient mice activated EMT, which is associated with CSC expansion and BLBC development. More p18;Brca1 or p16;Brca1 double mutant tumors expressed higher levels of Pdgfr, p-Pkc, and Fra1 than p18 single mutant tumors. Inhibition of Pdgfr or Pkc activity reversed EMT in Brca1 deficient tumor cells. We hypothesize that BRCA1 suppresses PDGFR-PKC-FRA1 signaling and collaborates with the INK4-CDK6 pathway to control CSCs and BLBCs. We propose two aims to test this: Aim 1: Determine the role of PDGFR-PKCFRA1 signaling in BRCA1 mediated tumor suppression, and Aim 2. Determine whether PDFGR-PKCFRA1 signaling collaborates with CDK6 to drive BRCA1 deficient CSCs and how BRCA1 regulates the assembly of FRA1-c-JUN complex. This proposal has two impacts: 1. Identifying PDGFR-PKC-FRA1 signaling as a downstream signaling of BRCA1 in the suppression of CSCs provides a new pathway to be therapeutically targeted for BRCA1 deficient tumors. 2. Discovering that CDK6 cooperates with PDGFR-PKC-FRA1 signaling to control CSCs allows two pathways to be targeted in BLBCs.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Shari Pilon-Thomas, Ph.D.	H. Lee Moffitt Cancer Center and Research Institute	Lymphodepletion-generated Myeloid Derived Suppressor Cells Decrease the Efficacy of Adoptive T cell Therapy for Melanoma	Melanoma is a leading cause of cancer mortality in the United States. Patients with melanoma and other cancers have immune cells (T cells) that are capable of recognizing and killing tumor cells. These T cells are ineffective due to suppressive factors in the cancer patient that allows tumors to "escape" from recognition by T cells. These factors include myeloid derived suppressor cells (MDSC) that actively shut off T cell responses. One strategy to improve immune responses against tumors is adoptive cell therapy (ACT) using tumor-specific T cells. In this strategy, T cells are isolated from patient tumors and expanded in the laboratory to high numbers. This process allows the T cells to become re-activated and capable of mediating tumor killing. The expanded T cells are transferred back to the patient. ACT with tumor-specific T cells has emerged as one of the most powerful therapies resulting in a 50% response rate in patients with unresectable metastatic melanoma. In order for this therapy to be effective, the patient must be treated with drugs that induce lymphopenia (depletion of circulating white blood cells). Induction of lymphopenia is important as it creates extra space for the transferred T cells to survive and proliferate. In addition, suppressive factors including MDSC are reduced during lymphopenia, allowing for maximum activity of transferred T cells. Lymphopenia is a temporary state and white blood cells will begin to repopulate the blood within a week after T cell transfer. Our preliminary results show that MDSC recover quickly after the induction of lymphopenia and are even more suppressive than prior to induction of lymphopenia. This rapid repopulation of highly suppressive MDSC may decrease the effectiveness of ACT by shutting off T cells and preventing complete tumor regressions. The research proposed in this application will improve the understanding of MDSC expansion and suppressive functions in the setting of lymphopenia and determine the effects of blocking MDSC expansion and function on T cell responses after ACT. The goals of this proposed research are threefold: 1. To evaluate the role of MDSC populations at the tumor site after induction of lymphopenia; 2. To define the factors that contribute to the rapid expansion and function of MDSC populations in the setting of lymphopenia; and 3. To examine the reconstitution and function of MDSC populations in melanoma patients enrolled in ongoing ACT clinical trials. Achievement of these goals will determine whether eliminating MDSC in the setting of lymphopenia is feasible to improve the activity of tumor-specific T cells. As a consequence of these studies, novel approaches based on MDSC blockade and ACT may result and improve therapies for patients with advanced cancers.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Jianguo Tao, M.D., Ph.D.	H. Lee Moffitt Cancer Center and Research Institute	Ibrutinib Resistance Mechanism in Mantle Cell Lymphoma	There are many types of cancers in the human body. The one we would like to study is a blood cancer called lymphoma. Most cancer patients with lymphoma are put on drugs called chemotherapy to help destroy cancer cells. There are many lymphoma patients who are on chemotherapy, but the chemotherapy is not helping them because the lymphoma cells become drug resistant. Mantle cell lymphoma (MCL) is a cancer that arises in lymphoid organs and an aggressive type of lymphomas. This type of lymphoma is often associated with an adverse prognosis, aggressive clinical fatal course and shortened survival due to drug resistance. There is evidence that shows there are interactions between cancer cells and the surrounding cells near them. We believe that these surrounding cells in the environment; have an important part, in how lymphoma cells develop and respond to chemotherapy and acquire secondary drug resistance. This study is designed to discover, how the surrounding environment affects the cancer cell growth and how lymphoma (MCL) responds to chemotherapy, so we can help lymphoma patients who are not usually being helped by chemotherapy.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Gaofeng Wang, Ph.D.	University of Miami	Epigenetic Prevention of Breast Cancer Progression by Vitamin C	Breast cancer is one common malignancy that predominantly affects women. The onset of breast cancer is the consequence of a combination of genetic and environmental risk factors, such as certain life styles and diets. Our laboratory recently found that vitamin C, a micronutrient, is essential for a group of enzymes termed TET to generate a special component named 5hmC in DNA. In many types of cancers, including breast cancer, 5hmC has been found at either a very low level or undetectable. The loss of 5hmC changes the functions of many genes, which contribute to the transformation of healthy breast cells into cancerous breast cells. Previous studies have shown that increasing the amount of the TET enzymes in breast cancer decreases its malignancy. While increasing TET level in patients might not be clinically feasible, finding a means to therapeutically restore normal 5hmC content may ultimately help reverse the malignant phenotype and yield a novel therapy for breast cancer. Vitamin C appears to conveniently restore 5hmC in the cell. In preliminary studies, we found that the vitamin C transporters are indeed low in most cases of human breast cancer, which would therefore cause a local vitamin C deficiency. 9 of 12 Treating breast cancer cells with vitamin C resulted in decreased invasiveness, inhibited cell growth along with an elevation of 5hmC content. Based on these promising results, this research proposes to test whether vitamin C can prevent the onset and progression of breast cancer, which addresses one of the Bankhead-Coley Cancer Research Program priorities: prevention and treatment. Successful completion of this research could help develop a novel prevention and treatment for breast cancer patients. If we can successfully reduce the malignancy of breast cancer in rodent models by repletion of vitamin C, this would support a similar therapeutic approach in breast cancer patients to delay or prevent disease progression.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Dinorah Martinez Tyson, PhD, MPH, MA	University of South Florida	Women at work: Multiethnic comparison of cancer survivors with low-status jobs	We have scant knowledge about work outcomes among women cancer survivors who were employed in low-status occupations at time of diagnosis. Work outcomes have substantial implications for their short- and long-term economic, physical and psychosocial well-being. We need to understand the underlying work environments that exacerbate health disparities and affect cancer morbidity, particularly among minority cancer survivors. This exploratory, developmental project stems from a strong partnership between academic team members, the Tampa Bay Cancer Community Network (TBCCN), a NCI Community Network Program to reduce health disparities and two community-based organizations, Faces of Courage and Latinos Unidos por un Nuevo Amanecer, Inc. (LUNA). Representatives from these organizations have voiced concerns about the work-related difficulties faced by women survivors and the lack of information and programs available to address these issues. The academic members of the research team have worked collaboratively with these organizations to develop relevant specific aims and proposed methodology. The study aims to: 1) Explore work-related decisions and the challenges experienced by cancer survivors who work in low-status occupations and 2) Develop a survivor and employer advisory board that will inform the research process and provide input that will strengthen the NIH proposal re-submission. The proposed qualitative study will advance knowledge about work environment, social context, and cultural factors that influence work-related challenges and employment status following cancer treatment among women cancer survivors in low-status occupations, with a focus on minorities. We will conduct interviews with a total of 30 women who were working in low-status jobs at the time of cancer diagnosis. We will include an equal number of Latina, African American and European American cancer survivors. We will be able to compare work-related experiences following a cancer diagnosis across three racial-ethnic groups. This will enable us to gain preliminary knowledge about post-diagnosis work experiences of diverse cancer survivors, and minorities in particular, who may be more vulnerable to loss of employment during the survivorship period. Findings will inform broader employment policies and procedures, and implications and application for future psycho-educational interventions and work-related training programs that engage and support cancer survivors.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
John Copland, PhD	Mayo Clinic Jacksonville	Novel Metabolic Target Induces Immunogenicity and Antitumor Synergy with Immune Checkpoint Inhibitor Leading to Survival Benefit	Recent studies have implicated lipid or fatty acid (FA) biosynthesis and desaturation as a requirement for tumorigenesis, survival and progression. A key mediator of FA biosynthesis, stearoyl CoA desaturase one (SCD1) is rate-limiting in the conversion of saturated fatty acids (SFA), such as oleic and palmitic acid, to monounsaturated fatty acids (MUFAs), palmitoleate and oleate, which are preferentially transformed into triglycerides for storage or phospholipids for membrane formation. SCD1 mRNA and protein are overexpressed in most aggressive cancers. Specifically, high SCD1 levels correlated with poor patient survival in breast cancer. Our published cell culture and animal model data demonstrated endoplasmic reticulum (ER) stress induced cell death as a mechanism of action for antitumor activity alone and in synergistic combination therapy. From these promising results, we developed four novel SCD1 inhibitors. Two lead SCD1 inhibitors bind SCD1 with EC50s of 1.9 and 29 nM with similar proliferation IC50 values. SSI-4 induced apoptotic cell death via ER stress across a wide range of cancer histotypes. The results led to a patent filing of novel composition of matter. We now show for the first time that inhibition of SCD1 increases the immunogenicity of poorly immunogenic tumors. The enhanced immune activation is accompanied by upregulated ER stress. Inhibition of SCD1 increased both recruitment and activation of immune cells in vivo, which when combined with PD-1 blockade resulted in potent and durable anti-tumor T cell responses in models of HER2 breast cancer. In the TUBO model, tumors were completely insensitive to anti-PD1 therapy but when combined with SSI-4, 80% of mice were cured. Thus, we discovered that aberrant de novo lipogenesis is linked to tumor immunogenicity, SCD1 inhibitors are immunosensitizing agents and SSI-4 may be used as an adjuvant therapy with other immunotherapies including checkpoint blockade. Together, our results indicate that inhibition of tumorigenic de novo lipogenesis represents a novel approach to enhance T cell based cancer immunotherapy. We propose to further develop SSI4 combination therapy with anti-PD1 and anti-PD-L1 immune checkpoint inhibitors using mouse models of breast and colon cancers and melanoma leading to a patent filing to protect and enhance commercialization potential of our SCD1 inhibitors. We also intend to file an investigation of new drug (IND) with the Federal Drug Administration (FDA) for SSI4 leading to clinical trials testing blockade of SCD1 and immune checkpoint as a therapeutic strategy to enhance survival in cancer patients. To reach these goals, we propose three aims: (1) demonstrate antitumor synergy and survival benefit of SSI-4 in combination with anti-PD1 and anti-PD-L1 antibody in triple negative and HER2+ breast cancers as well as colon cancer and melanoma, (2) examine mechanisms of action whereby SSI-4 sensitizes tumors to checkpoint inhibitors, (3) write a clinical trial. In summary, we are developing novel SCD1 inhibitors which are currently not in development for the treatment of cancer. We predict that these inhibitors will find broad applicability and benefit patient survival, especially in cancer populations where immune checkpoint inhibitors are not effective.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Brian Ruffell, Ph.D.	H. Lee Moffitt Cancer Center	Regulation of Dendritic Cell Function and Tumor Immunity by TIM-3	Tumor immunity is predicated upon the de novo activation and expansion of antigen-specific cytotoxic T lymphocytes. However, to impact tumor growth these T cells must also infiltrate into tumors, overcome a suppressive environment, and avoid becoming exhausted in the presence of persistent antigen, barriers that are thought to be major impediments to immunotherapy. Conventional dendritic cells are well established as the central inducers of the adaptive immune response, but emerging evidence suggests they may also play in supporting T cell activity within peripheral tissues, including tumors. In support of this, we have found in preliminary studies that TIM-3 (T-cell immunoglobulin and mucin domain containing-3) is highly expressed by tumor dendritic cells, and that TIM-3 blockade induces expression of the chemokine CXCL9 in vitro and in vivo, thereby promoting T cell cytotoxic effector function in models of mammary (breast) carcinoma. Here we propose to identify the dendritic cell activation pathways altered by TIM-3, determine if non-migratory dendritic cells maintain T cell function within tumors, and determine the role of CXCL9 expression by dendritic cells in tumor immunity. These studies will delineate a putative dendritic cell regulatory pathway and improve our understanding of the role of dendritic cells within tumors, both factors that may have important implications for the design of combinatorial immunotherapies in breast cancer.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Keiran Smalley, Ph.D.	H. Lee Moffitt Cancer Center	Defining and Therapeutically Targeting HDAC8-driven Reprogramming in Melanoma Brain Metastasis Development	The long-term goals of this research program are to develop strategies that improve the survival of patients with advanced melanoma, the most deadly form of skin cancer. Among all tumor types, melanoma has a high likelihood of spreading to the brain. Brain metastasis occurs in ~30% of melanoma patients (as high as 75% at autopsy), and the brain is often the major site of treatment failure for patients who otherwise responded well to current FDA-approved melanoma therapies. A new therapy that prevented melanoma cells from growing in the brain would allow our patients to live for longer and have a better quality of life. We currently do not understand how melanoma cells spread to the brain and this limits our ability to develop new therapies for this devastating complication of advanced melanoma. New research will help address this gap in our understanding. In order to spread to the brain, melanoma cells escape from the primary tumor and enter the blood (which is typically a hostile environment for cancer cells) and then survive for long enough to reach the brain. Once in the blood supply of the brain, the melanoma cells stick to the blood vessels and then crawl through small gaps in the vessel walls to enter the brain. We believe that the melanoma cells that can do this have special molecular properties, which may also make them vulnerable to new drugs. In preliminary studies, we uncovered a "molecular switch" called HDAC8 that reprogrammed the melanoma cells to survive for longer in the circulation (the veins and arteries) by increasing their physical toughness and allowing them to move more efficiently through the blood vessels into the brain. We believe that this new cellular "program" we identified could be the key to preventing patients from developing new melanomas in their brains. Our proposal has three key goals. 1) To map out the special cellular "program" that makes the melanoma cells more tough, this will allow us to identify new therapeutic targets in these cells 2) determine how this cellular program changes the behavior of melanoma cells so they can survive in the blood vessels and then crawl through the blood vessels and enter the brain 3) test new drugs that kill the melanoma cells with the "brain homing" properties and determine whether the new therapy can be used in combination with established melanoma therapies that either kill the melanoma cells directly or stimulate the immune system to kill melanoma cells.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Robert J. Gillies, Ph.D.	H. Lee Moffitt Cancer Center	Targeting the Lipogenic Phenotype Induced by Extracellular Acidosis in Breast Cancer	Solid tumors are unequivocally acidic due to elevated rates of glucose fermentation coupled with poor perfusion. Tumor microenvironmental acidity has been shown to promote local invasion, metastasis, and resistance to immune surveillance. It is axiomatic that adaptation to this acidic microenvironment is essential for tumor cells to survive and thrive and further, to out-compete the stroma into which they invade. In prior work, published in Cancer Research and Nature Communications, we have shown that acid adaptation is associated with chronic activation of autophagy and redistribution of the lysosomal proteins to the plasma membrane. These interrelated processes are key survival mechanisms adopted by tumor cells under acidic conditions. In subsequent studies (manuscript in preparation), we have also observed that acid adaptation is accompanied by a robust and dramatic increase in the accumulation of cytoplasmic lipid droplets ("adiposomes"). We hypothesize that adiposomes are coupled to autophagy and lysosomal redistribution and, hence, adiposome formation is a rapid readout for these other processes that together form an acid adaptation network. This has been observed in prostate, melanoma, lung, cervical, and breast cancer cells, as well as normal fibroblasts. Adiposomes are known in other organ systems (e.g. NASH and FLD in liver) to be induced under metabolic stress. They are dynamic organelles that store neutral lipids surrounded by a shell of proteins (perilipins) and a phospholipid monolayer. Notably, perilipin expression is a negative prognostic indicator in breast and ovarian cancers. Although a lipogenic phenotype is frequently observed in cancer, little is known about why they accumulate in acidic conditions or how acid signal perceived at the cell surface results in accumulation of lipid droplets. To identify if plasma membrane acid sensors are involved in transducing the signal, we used CRISPR/Cas9-mediated depletion of major acid-sensing G-protein coupled receptors (GPCRs) in breast cancer: TDAG8 and OGR1. In both MCF7 and T47D cells, we observed that OGR1 (but not TDAG8) depletion inhibited acid-induced adiposome accumulation. In this proposal we will explore signaling downstream of OGR1 and functionally characterize OGR1 knockout cells to unravel the entire signaling cascade. We have also shown that acid-induced accumulation of lipid droplets persists even when cells were in de-lipidated serum, indicating de novo synthesis. Indeed, 13C tracer studies indicate that ketogenic amino acids resulting from autophagic protein degradation are the primary source of carbons for de novo synthesis in adiposomes. Paradoxically, fatty acid synthesis appears to occur contemporaneously with lipid β oxidation (βox), indicting a high turnover of adiposomes. Notably, inhibition of fatty acid synthesis or βox selectively killed cells under acidic, compared to neutral, conditions hence, this has identified a novel therapeutic vulnerability. We propose to further characterize the mechanisms controlling these metabolic pathways using gene editing incombination with 13C tracer metabolite analyses of fatty acid synthesis and degradation. Finally, we will assess if adiposomes are associated with acidosis and/or aggressiveness using mouse models and human tissue micro arrays. We believe that the proposed studies will shed light on novel aspects of cancer biology and identify further new therapeutic opportunities.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Otto Phanstiel, PhD	University of Central Florida	Developing Polyamine Transport Inhibitors for the Treatment of Human Cancers	The long-term objective of this project is to develop new cancer therapeutics. We are focused on pancreatic cancer because it is the fourth-leading cause of cancerrelated death and has a shockingly-low five-year survival rate of <8%. As such new medicines are desperately needed. The most common pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC). We have discovered a unique protein signature which indicates which PDAC tumors have high polyamine transport activity. We hypothesize that these tumors are driven to maintain high levels of intracellular polyamines by the genetic mutation in the Kras gene which occurs in the vast majority of PDAC cases. This makes sense because polyamines are important growth factors for cells and play critical roles in translation, transcription and chromatin remodeling. The high polyamine levels are maintained via increased polyamine biosynthesis and up-regulated polyamine import. The danger to the tumor is polyamine overload as the native polyamines can become toxic to the cell at high concentrations. The tumor avoids this danger by exporting polyamines into the surrounding tumor microenvironment. This has consequences. For example, secreted polyamines like spermine can inhibit immune cells from mounting a proper immune response. We speculate that polyamine exchange between tumor and stroma creates a zone of high polyamine concentration near the tumor. This polyamine 'shield' provides immune privilege because the approaching immune cells are compromised, when they import spermine. Indeed, this is a fetal strategy because spermine is present at high levels in amniotic fluid to protect the developing fetus from maternal immune cells. We believe that PDAC uses this fetal strategy, a spermine shield, to temper the immune response. There is solid evidence which suggests that immune cells (e.g., T cells, NK cells, macrophages) with high polyamine content have dramatically reduced ability to fight the tumor. In short, the tumors' polyamine trash is used to inhibit the immune response and is also recycled by the stroma and used to cross feed the tumor. This creates a zone of immune privilege which the tumor uses to survive and grow. Our approach is to develop new medicines (polyamine transport inhibitors, PTIs) which block the import of polyamines into cancer cells. These compounds when used with a polyamine biosynthesis inhibitor will starve the tumor of its polyamine growth factors and eventually shunt the tumor to programmed cell death (apoptosis). The project will also explore how polyamine transport genes are regulated and respond to external polyamine stimuli. An increased understanding of these transport response processes could also lead to new drug targets. Lastly, we will evaluate the new medicine in two mouse models of pancreatic cancer to show that this therapeutic approach works in vivo as well as on ex vivo human PDAC samples. The PTIs are owned by UCF and there are no impediments in terms of intellectual property rights and commercialization. A success here will provide a new combination therapy for pancreatic

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Barry Hudson, Ph.D.	University of Miami	Therapeutic Targeting of RAGE in Breast Cancer Progression and Metastasis	The metastatic spread of breast cancer cells is the leading cause of cancer death, and therefore identifying new ways to treat metastatic breast and other carcinomas is imperative. We have shown that the Receptor for Advanced Glycation End-products (RAGE) and its ligand are a critical pathway underlying breast cancer pathogenesis. Human studies have revealed RAGE protein levels are increased in aggressive breast cancers, and higher levels of RAGE are predictive of worse breast cancer outcomes. Our preliminary and published data suggest RAGE drives key molecular processes leading to tumor invasion and metastasis. Further, in both xenograft and syngeneic mouse models of breast cancer, we have shown RAGE signaling drives malignancy through effects on cells of both the tumor and its surrounding stroma. Most importantly, we show for the first time that novel small molecule inhibitors of RAGE powerfully suppress breast cancer metastasis in mouse xenograft models. Therefore, further preclinical testing and validation of RAGE inhibitors are critical before translation to people with breast cancer. The current Technology Transfer Feasibility application aims to perform extensive testing and validation in animal models of breast cancer, in order to advance our novel RAGE inhibitors to clinical trials. Further the data generate from these studies will greatly improve the commercial viability of RAGE inhibitors. We will use multiple animal models and extensive ex vivo analysis to assess the efficacy of RAGE inhibitors. These will include patient derived breast cancer xenograft models, syngeneic mouse models (in different mouse strains; C57BL6 and BALBc), and spontaneous mammary mouse tumor models. Successful completion of this study will not only help understand how breast and other cancers metastasize, validate RAGE inhibitors in preclinical models, but also help in the translation to human clinical trials by improving their commercial value. Thus, the proposed research is highly relevant to the Florida BRAC mission and research priority areas which pertain to the understanding of the causes of breast cancers, the development of novel treatments, and their ultimate translation to clinical practice.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Ashok Saluja, Ph.D.	University of Miami	Role of Microbiome in Modulating Liver Metastases in Colon Cancer	Metastases or the consequence of their treatment are the biggest contributor to death from cancer. Colorectal cancer is no different. In 2017 about 140,000 people will be diagnosed with colon and rectal cancer in United States. Out of which about 50% will be diagnosed with metastases, either at presentation or during the course of their disease. Thus, there is an urgent need to better understand the process of metastases and develop novel treatment strategies. Unfortunately, our understanding of the process of metastases is still rudimentary. For instance, it is unclear why certain organs are more prone to metastases as compared to others. While mechanical factors such as blood flow and lymphatic drainage pattern are certainly at play, cancer cells demonstrate tropism to certain organs for metastatic growth. In this regard liver is the most common site of liver metastases from colon and rectal cancer. Better understanding of why liver is such a favorable organ for metastases will lead to development of targeted therapies. Liver is believed to be an immune-privileged organ which favors the induction of tolerance than induction of immunity. Whether, this immune-tolerant phenotype contributes to the preponderance of metastases in liver is unknown. Furthermore, the reason why liver is an immunotolerant organ is unclear. Our preliminary data suggest that gut microbiome is responsible for creating an immunosuppressive environment in the liver. In our studies depletion of gut-microbiome with antibiotics prevents growth of liver metastases. We have also observed that depletion of microbiome is unable to inhibit liver tumor growth in a mouse lacking adaptive immunity suggesting that adaptive immune system is required for modulation of liver metastases by microbiome. Furthermore, T cells obtained from the animals after gut microbiome depletion are very effective in killing cancer cells. Based on this and other literature we have hypothesized that exposure to gut microbial antigens causes immunotolerances and creates a permissive environment for the metastatic colon cancer cells to grow. In the current grant-proposal, we will test this novel hypothesis. In aim 1 using models of colon cancer liver metastases and using antibiotics induced microbiome depletion, use of germ free mice and use of probiotics we will establish that microbiome modulates liver metastases. In aim 2, using immune profiling and animal experiments we will establish that the reduced liver metastases growth observed on depletion of microbiome is dependent on T cells. And finally, in aim 3, we will evaluate the mechanism by which gut microbiome modulates immune cells in the liver to create an immunosuppressive environment. These innovative studies will provide potential therapeutic breakthrough in treating colon cancer liver metastases by modulating entero-hepatic axis by routine antibiotics, probiotics or by targeting novel pathways identified in this research.

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David Robbins, PhD	University of Miami	Targeting Wnt-dependent colorectal cancer	Constitutive activation of WNT signaling drives the growth of a broad array of human tumors, including nearly all colorectal cancers (CRCs). Despite this prominence, no Wnt inhibitors are currently approved for clinical use. The major reasons for this lack of inhibitors are the paucity of druggable WNT pathway components and the on-target gastrointestinal (GI) toxicity observed in animal models with many candidate inhibitors. Our results show that reduced expression of Casein Kinase 1α(CK1α), a negative regulator of Wnt signaling, is associated with decreased survival of CRC patients. These findings validate CK1α as a druggable target in CRC. We therefore characterized a novel, small molecule activator of CK1α, SSTC3, with pharmacokinetic properties that would allow us to target CK1α in vivo. SSTC3 attenuated CRC growth in vitro and in vivo, prolonging the survival of a mouse colorectal tumor model and inhibiting the growth of CRC xenografts. Importantly, SSTC3 did not exhibit significant GI toxicity. Thus, CK1α is a bona fide druggable target in CRC, activation of which inhibits tumorigenesis without inducing the GI toxicity that has hampered the clinical development of Wnt inhibitors. Despite this promise, many mechanistic questions remain regarding this novel class of Wnt inhibitors, which we will begin to address here. Specifically, we propose to i) determine how this class of small-molecules functions to activate CK1α activity, ii) identify the CK1α substrates that drive its efficacy but limit its effect on normal GI homeostasis, and iii) develop biomarkers that could be used to identify those CRC patients most likely to respond favorably to such inhibitors.

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Eric Wieder, PhD	University of Miami	Multiplex Imaging Resource for Florida State	In order to develop new treatments for cancer, and to better understand which cancer patients will benefit from a specific treatment, more sophisticated tools are continually being invented. These new technologies allow doctors and scientists to gain increasingly complex information on each person's cancer and will ultimately allow us to customize therapy to best benefit each patient and to provide the best possible outcomes. One such tool is the ability to look at tumor samples under the microscope and determine which cell types are in a tumor, what unique markers are on those cells and how other cell types within the tumor are interacting with it. This is done by taking a slice of tumor (biopsy), and staining it on a slide and then taking a magnified picture of it using a microscope. There are various staining methods which allow pathology labs to identify various characteristics of tumors, but a more sophisticated way uses antibodies tagged with colors to be able to distinguish different markers on cells within the tumor. In most labs, it is typical to be able to look at 1-4 markers at the same time, although there is specialized equipment that can look at 10-12 at a time. A recently developed technology uses metal atoms instead of colors to tag and identify each marker, which has increased the number of markers that can be studied simultaneously to 50 markers or more. This technology was commercialized to look at single cells, but not tumor biopsies, within the last decade. More recently, this tool was modified to allow it to work to image cells in a tumor biopsy. Although there are over 60 installations of the recently developed single cell technology at academic and government research centers across the USA, and 30 installations of the new tumor imaging technology across the world, there are none for either single cells or tumors in all of Florida. This disruptive technology has begun to be used by scientists all over the world and results are beginning to be published. If we purchase this new equipment, it will be able to be used both for tissue samples and for cells in a suspension. We have numerous labs at University of Miami and at Moffitt Cancer Center which have identified this technology as useful for their research. Creating this Imaging Center, which will be open to all cancer investigators in Florida, will greatly enhance our ability to stay competitive in the developing areas of cancer research since soon, it will be required that these complex measurements will be included in any study that involves either heterogeneity of tumors (differences within them), or immune therapy.

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Shanta Dhar, PhD	University of Miami	Multifunctional Nanoparticle for Targeted Combination Therapy of Prostate Cancer	Prostate cancer is the second leading cause of death in American male population. Prostate cancer at an early stage may be cured by surgery and/or radiation therapy. However, the advanced castration-resistant prostate cancer is difficult to treat with currently available therapies. The use of a single therapeutic modality has limited success since several factors, inflammation, resistance, bone metastases, and participation of metabolically altered cancer stem cells (CSCs) play integral roles for progression and spread of this disease. We have developed a multifunctional polymer-based nanoparticle (NP) technology which has the ability to deliver a predefined stoichiometric combination of chemotherapy, anti-inflammatory dose, and an inhibitor of bone metastasis in a spatio-temporal and targeted manner to prostate cancer. More recently, we found that low-dose irradiation further sensitizes the activity of this targeted multifunctional platform towards prostate-specific membrane antigen (PSMA) expressing advanced prostate cancer cells. Under ionizing radiation condition, this NP system was able to modulate mitochondrial metabolism and fatty acid oxidation-based respiration of PSMA expressing prostate cancer cells. Based on these results, we now formulated the current project combining several unique strengths offered by a highly integrated and interdisciplinary team and strong preliminary data to provide a platform with ability of loading multiple drugs with a predefined stoichiometric ratio for targeted co-delivery of chemotherapeutics, anti-inflammatory agents, and inhibitors of bone resorption to metastatic prostate cancer attacking PSMA expressing cancer cells, tumor associated inflammation and simultaneously reducing bone metastasis and inhibiting mitochondrial respiration, ATP production in CSCs forcing this population to undergo apoptosis, and evaluating this platform in patient derived prostate cancer preclinical model. Successful completion of the proposed aims will allow us to discover a therapeutic modality for treating metastatic prostate cancer, a major unmet clinical need.

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Carlos Perez-Stable	University of Miami	A New Strategy to Increase Proteotoxic Cell Death in Prostate Cancer	Prostate cancer is a leading cause of death in men and when unresponsive to androgen deprivation therapy, it is known as castration-resistant prostate cancer (CRPC). Enzalutamide is a new approved drug that inhibits androgen receptor activity and increases overall survival. However, most responding patients develop resistance to enzalutamide, indicating that new therapies are required to block CRPC. We propose a new strategy that increases proteotoxic stress with cyclophilin + proteasome inhibitors to promote apoptotic cell death in CRPC without toxic side effects. We discovered a new chemotherapy strategy using an inhibitor of proteins in the cyclophilin family (CRV431) combined with inhibitors of the main protein degradation pathway, the proteasome (carfilzomib, ixazomib). Cyclophilins are required for proper folding of proteins so inhibitors of cyclophilins will increase misfolded proteins, which will further accumulate when combined with proteasome inhibitors to amplify proteotoxic stress and lead to cancer cell death. Our preliminary data in CRPC and other cancer cells support the new CRV431 + carfilzomib combination chemotherapy strategy. Because the proteotoxic stress protective mechanism is already highly activated in cancer compared to normal cells, further increasing proteotoxic stress will have an irreversible lethal effect. Therefore, drug combinations that maximize proteotoxic stress may prove to be selectively toxic to cancer cells. Our preliminary data is supportive of the idea that the new CRV431 + carfilzomib combination is more toxic to cancer cells including CRPC compared to non-cancer cells. The hypothesis of this 6-month bridge mechanism proposal is that the combination of cyclophilin (CRV431) and proteasome (carfilzomib, ixazomib) inhibitors will amplify proteotoxic stress, overwhelm the pro-survival pathway, and force CRPC cells including resistant to current therapies towards apoptotic cell death without harming normal cells. The rationale is that if this new combination kills CRPC cells without harming normal cells in preclinical models, the chances for success in clinical settings will increase. Aim 1: Identify the potential mediators of CRPC cell death in the cyclophilin + proteasome inhibitor combination. Aim 2: Determine if the cyclophilin + proteasome inhibitor combination has toxicity in non-cancer cells. New androgen receptor targeting agents have improved survival in some CRPC patients, although resistance is a major limitation. We propose that targeting the essential proteotoxic stress response survival pathway by combining cyclophilin and proteasome inhibitors will be a useful strategy to selectively kill CRPC without causing excessive side effects to normal cells and tissues. Currently, cyclophilin inhibitors such as CRV431 are being investigated as anti-viral agents and we are the first to propose its use in CRPC therapy. The long-term goal will be to use orally bioavailable CRV431 + ixazomib combination to treat CRPC patients with the hope that proteotoxic stress cell death specifically in CRPC cells without causing toxicity to normal tissues will increase overall survival and improve quality of life.

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