CANCER RESEARCH SYMPOSIUM

Tuesday, January 10th

9:00AM—4:30PM

Research resulting from the

Bankhead-Coley Cancer Research Program

MOFFITT CANCER CENTER RESEARCH AUDITORIUM

Florida HEALTH MOFFITT CANCER CENTER

CANCER RESEARCH SYMPOSIUM: WELCOME

9:00 AM	**Welcome and Overview of the Symposium**	**Patrick Hwu, MD** Chief Executive Officer, Moffitt Cancer Center
		John Cleveland, PhD Director, Moffitt Cancer Center
9:10 AM		**Joseph A. Ladapo, MD, PhD** State Surgeon General
9:25 AM		**Daniel Armstrong, PhD** Chair, Biomedical Research Advisory Council (BRAC) and Moderator

CANCER RESEARCH SYMPOSIUM: DISCOVERY SCIENCE

9:30 AM – 10:40 AM	**Discovery Science**	**Nicholas Lawrence, PhD.** Moffitt Cancer Center/University of South Florida *Novel monovalent and bivalent JAK2 inhibitors for targeted MPN and cancer therapies*
		John Copland, PhD Mayo Clinic Jacksonville *Novel metabolic target induces immunogenicity and antitumor synergy with immune checkpoint inhibitor leading to survival benefit*
		Stephan Schurer, PhD for Kelly Burnstein, PhD University of Miami *Data-Driven Approaches Targeting Prostate Cancer*

10:40 AM	**Break & Poster Session**

CANCER RESEARCH SYMPOSIUM: CLINICAL RESEARCH

11:00 AM – 12:30 PM	**Clinical Research & Research Infrastructure**	**Carlos Perez-Stable, PhD** South Florida Veterans Affairs Foundation for Research and Education, Inc. *A New Strategy to Increase Proteotoxic Cell Death in Prostate Cancer* **Gina M. DeNicola, PhD** Moffitt Cancer Center/University of South Florida *Therapeutic Strategies for KEAP1/NRF2 Mutant Lung Cancer* **Kathleen Egan, ScD** Moffitt Cancer Center/University of South Florida *Biobanking for Breast Cancer Prevention and Disparity Research in Florida* **Curtis Lisle, PhD, presenting for Ulas Bagci, PhD** University of Central Florida *Predicting Outcomes of Lung Cancer Therapy Through Explainable Deep Learning*

12:30 PM – 1:30 PM	**Lunch on Your Own – Cafeteria Available**

CANCER RESEARCH SYMPOSIUM: PANEL PRESENTATION

1:30 PM – 2:30 PM	**Casey DeSantis Cancer Research Program, Florida Consortium of National Cancer Institute Centers (FACCA) – Panel Presentation**	**John Cleveland, PhD** Moffitt Cancer Center **Jonathan Licht, MD** University of Florida Health Cancer Center **Stephen D. Nimer, MD** University of Miami Sylvester Cancer Institute

CANCER RESEARCH SYMPOSIUM: PREVENTION & TREATMENT

2:30 PM – 3:10 PM	**Prevention & Treatment**	**Matthew Schabath, PhD** Moffitt Cancer Center/University of South Florida *Non-invasive Adiomic Biomarkers to Predict Treatment Response for Immunotherapy of Lung Cancer* **Thomas Malek, PhD** University of Miami *CD4+ T effector cells in cancer immunotherapy*

For more information on presentations please visit
www.flhealth.gov

3:10 PM	**Break & Poster Session**	
3:30 PM – 4:15 PM	**Prevention & Treatment, Continued**	**Shanta Dhar, PhD** University of Miami *Multifunctional Nanoparticle for Targeted Combination Therapy of Prostate Cancer* **Clement K. Gwede, PhD** Moffitt Cancer Center/University of South Florida *Community CARES: A Multilevel Intervention to Increase Colorectal Cancer Screening Adherence in Community Clinics*

CANCER RESEARCH SYMPOSIUM: CLOSING REMARKS

4:15 PM	**Closing Remarks**	**Daniel Armstrong, PhD** Biomedical Research Advisory Council (BRAC) Chair, and Moderator

Poster Session Abstracts

Dr. Junko Sawada, DVM, PhD for Masanobu Komatsu, PhD
Johns Hopkins All Children's Hospital
Reprograming Tumor Immune Landscape by High Endothelial Venule Formation

Elias Sayour, MD, PhD
University of Florida
Lipid-nanoparticle vaccines targeting metastatic lung cancer from osteosarcoma

Valery Chavez PhD for Jaime Merchan, MD
University of Miami
Tumor and Stromal Targeted Oncolytic Virus Based Biotherapies for Colorectal Cancer

Paulo S. Pinheiro, PhD
University of Miami
Etiology, and Mortality for Highly Fatal Cancers in Diverse Florida; Unique Impact on African Americans, Afro-Caribbeans, Cubans, Puerto Ricans, and Other Hispanics

Andrew Judge, PhD
University of Florida
Ursolic Acid as a Countermeasure to Cancer Cachexia

Esther Guzman, PhD
Florida Atlantic University
Discovery of Marine Natural Products Active Against Triple Negative Breast Cancers Using 3-D - spherioid Cultures: An In Vivo Relevant Assay Platform

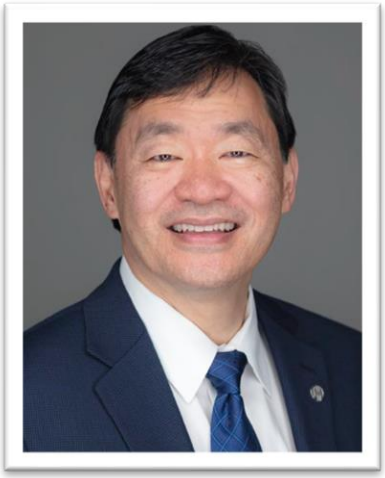
John Koomen, PhD
Moffitt Cancer Center
Proteogenomics of Metastatic Heterogeneity and Therapeutic Resistance in Lung Cancer

Lixin Wan, PhD
Moffitt Cancer Center
Characterizing oncogenic function of ITCH in melanoma

Map of Moffitt Cancer Center can be found at the end of the program

Opening Remarks

The Florida Department of Health and Moffitt Cancer Research Center are proud to be hosting this Cancer Research Symposium with the aim of bringing together thought leaders from throughout the state to discuss, explore, and share discoveries made in cancer research.



Patrick Hwu, MD
President & CEO of Moffitt Cancer Center

Patrick Hwu, MD, is the president and CEO of Moffitt Cancer Center, one of the nation's leading cancer hospitals and the only National Cancer Institute-designated comprehensive cancer center based in Florida.

As an internationally recognized tumor immunologist, Dr. Hwu has led pioneering research and clinical efforts to better understand the interactions between tumors and the immune system. He helped launch the field of gene modified T cells, publishing research on the first chimeric antigen receptor directed against cancer. His work focuses on vaccines, adoptive T cell therapies and immune resistance. An internationally recognized physician scientist, Hwu has a proven track record leading collaborative teams to make breakthroughs in science while improving cancer outcomes for cancer patients.

Prior to joining Moffitt, Dr. Hwu was the head of the Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center, where he held various leadership roles for 17 years. In 2003, he was recruited as the first chairman of the Department of Melanoma Medical Oncology. He was also the associate director of the Center for Cancer Immunology Research (2004) and chair of the Department of Sarcoma Medical Oncology (2012).

Dr. Hwu earned his medical degree from The Medical College of Pennsylvania. He served as a house officer in Internal Medicine at The Johns Hopkins Hospital and completed a fellowship in oncology at the National Cancer Institute, where he worked as a principal investigator leading tumor immunology studies.

John Cleveland, PhD
Executive Vice President, Moffitt Cancer Center Director

Moffitt Cancer Center is one of 53 National Cancer Institute (NCI)-designated comprehensive cancer centers in the country and the only one based in Florida.

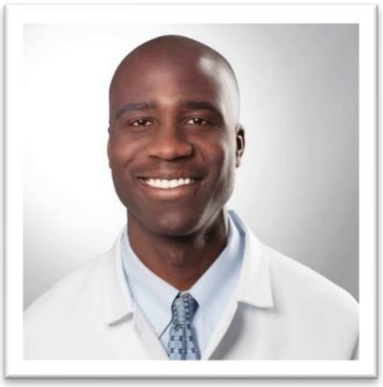
Dr. Cleveland is responsible for elevating Moffitt's research enterprise and reputation for world-class bench-to-bedside science. Dr. Cleveland will set the strategy and vision for research, overseeing 100 research labs and approximately 175 renowned

faculty at Moffitt. Dr. Cleveland is the principal investigator of Moffitt's Cancer Center Support Grant, which brings in approximately $3 million in NCI funding by delivering transdisciplinary science and driving impact locally, regionally, and beyond.

Dr. Cleveland's research interests include cancer cell checkpoints, cancer cell metabolism, cancer prevention and therapeutics, and the regulation and role of apoptosis and autophagy in the development and maintenance of cancer.

Dr. Cleveland is an exceptional scientist and leader, bringing 40 years of experience to this role. Dr. Cleveland joined Moffitt in 2014 as associate center director of Basic Science. Prior to Moffitt, Cleveland was professor and chair of the Department of Cancer Biology at The Scripps Research Institute. Dr. Cleveland also held various leadership roles with St. Jude Children's Research Hospital. Dr. Cleveland began his career working with the NCI, the federal agency charged with leading the National Cancer Program.

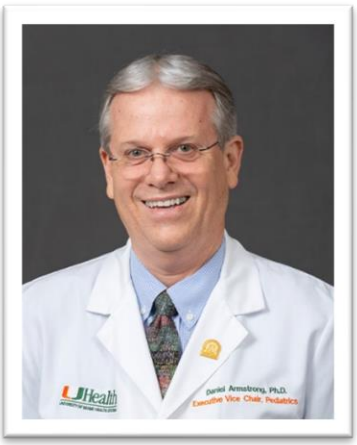
Dr. Cleveland is a member of the American Association for Cancer Research and the American Society of Hematology. Dr. Cleveland is a Moffitt Distinguished Scholar and holds the Cortner-Couch Endowed Chair for Cancer Research from the University of South Florida School of Medicine. Dr. Cleveland earned his bachelor's degree in biology from the University of Maine and his doctorate in immunology and microbiology from Wayne State University School of Medicine.



Joseph A. Ladapo, MD, PhD
State Surgeon General

Joseph A. Ladapo, MD, PhD, is the State Surgeon General of Florida. He also serves as Professor of Medicine at the University of Florida, where his research examines behavioral economic strategies to reduce cardiovascular risk in low-income and disadvantaged populations. Clinically, he has cared primarily for hospitalized patients. His research program has been supported by the National Institutes of Health and Robert Wood Johnson Foundation, and includes clinical trials of interventions for weight loss, smoking cessation, and cardiovascular disease prevention among people with HIV. Dr. Ladapo's studies have been published in leading medical journals, including The Journal of the American Medical Association, Journal of the American College of Cardiology, and Annals of Internal Medicine. His writings about health policy and public health have appeared in the Washington Post, Wall Street Journal, and USA Today. Prior to joining the faculty of University of Florida, he was a tenured Associate Professor at David Geffen School of Medicine at the University of California, Los Angeles (UCLA)

Dr. Ladapo graduated from Wake Forest University and received his medical degree from Harvard and PhD in Health Policy from Harvard Graduate School of Arts and Sciences. He completed his clinical training in internal medicine at the Beth Israel Deaconess Medical Center, where he received the Harvard Medical School Class of 2012 Resident Teaching Award and the Daniel E. Ford Award in Health Services and Outcomes Research from John Hopkins University.



Daniel Armstrong, PhD
Biomedical Research Advisory Council (BRAC) Chair, and Moderator

Professor & Executive Vice Chair, Pediatrics
Director, Mailman Center for Child Development
University of Miami Miller School of Medicine

Dr. Armstrong received his PhD in clinical/clinical child psychology at West Virginia University in 1985 following completion of a clinical internship in pediatric psychology at the University of Oklahoma Health Sciences Center. Dr. Armstrong joined the faculty of the University of Miami in 1985, and in 1999 was named Director of the Mailman Center for Child Development, the University of Miami's second center and only center with federal statutory designation. Over the past 37 years, Dr. Armstrong has served in multiple senior clinical, research, educational (LCME, GME, graduate, and research training), and administrative leadership roles in the Department of Pediatrics and Miller School of Medicine and was the Senior Vice President/CEO for the Holtz Women's and Children's Hospital for two years. Dr. Armstrong served as interim Senior Associate Dean for Faculty Affairs from 2014-2019, and Senior Associate Dean for Child Health for the Miller School of Medicine from 2019-2021.

Throughout his career, Dr. Armstrong's research has focused on describing neurodevelopmental outcomes of treatment of childhood cancer, sickle cell disease, and HIV/AIDS, understanding the mechanisms associated with these outcomes, and conducting clinical trials of interventions (behavioral, biological, and pharmacological) with children with neurodevelopmental disabilities and chronic illnesses. Most of his research has involved interdisciplinary and multi-center collaboration. Trained as a behavioral scientist, Dr. Armstrong has also established strong collaborations with basic, discovery, and clinical scientists on translational research questions. Dr. Armstrong has served as part of the scientific leadership of a number of NCI and The National Heart, Lung, and Blood Institute (NHLBI) multi-center clinical research trials, as chair of the NHLBI's Congressionally-mandated Sickle Cell Disease Advisory Committee, Chair of the Psychology and Behavioral Sciences Committees for both the Pediatric Oncology Group and Children's Oncology Group, was a member of the NCI Physician Data Query (PDQ) Supportive Care Editorial Board, PI of a five-year Dyson Community Pediatrics Training Initiative grant, and PI of a K30 that led to the establishment of a Master's of Science in Clinical and Translational Investigation at the University of Miami (UM).

Dr. Armstrong has served as a consultant to multiple federal agencies, including several institutes of the NIH, FDA, Health Resources and Services Administration (HRSA)/Maternal and Child Health (MCHB), National Academy of Sciences, Institute of Medicine (IOM/NAS), and the Executive Office of the White House. With more than 115 peer-reviewed publications and book chapters, Dr. Armstrong is author or contributing author of more than 15 policy statements for the American Academy of Pediatrics and other leading national organizations. Dr. Armstrong represents the American Cancer Society on the

Opening Remarks

Florida Biomedical Research Advisory Council (BRAC; Florida Department of Health), where Dr. Armstrong has served as Chair since 2013. In this role, Dr. Armstrong led the development of the state strategic research plan for cancer and tobacco-related diseases.

Dr. Armstrong has been actively involved in leadership of national, state, and local organizations related to developmental disability and chronic illness, including the American Cancer Society (ACS), Inc., where Dr. Armstrong served as Chair of the Florida Division Board of Directors and subsequently on the National ACS Board of Directors. Dr. Armstrong was the recipient of the 2005 Micah Batchelor Award for Excellence in Child Health Research, and the American Cancer Society Lane Adams Quality of Life Award (2009) and St. George Award (2015). For more than 20 years, Dr. Armstrong has been active in governmental public policy and appropriations related to child health and funding for cancer research at the state and federal levels, as well as philanthropy initiatives with major donors. Dr. Armstrong is the current President of the Association of University Centers on Disability, Co-Chair of the National Center for Advancing Translational Sciences (NCATS)/Clinical and Translational Science Award (CTSA) Integration Across the Lifespan Enterprise Committee, Vice-Chair of the Early Learning Coalition of Miami-Dade/Monroe, and past-president of the Florida Association of Children's Hospitals.

Discovery Science

Novel monovalent and bivalent JAK2 inhibitors for targeted MPN and cancer therapies

Nicholas Lawrence, PhD
Moffitt Cancer Center/University of South Florida

Myeloproliferative neoplasms (MPNs) are chronic leukemias composed of three main phenotypes including polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). MPN prevalence estimates that over 300,000 US patients live, equating to 21,000 Floridians with the disease and all of patients with PV having mutations in a protein called Janus kinase 2 (JAK2) and 60% of MF and ET patients having a JAK2 mutation. For this reason, developing new drugs to target JAK2 for treating myeloid cancers is of critical importance to Florida and the US.

The project team is using an interdisciplinary approach towards the development and characterization of new inhibitors of JAK2 and therefore of MPNs using medicinal chemistry, biochemistry and cell and animal models to improve efficacy and effectiveness over current clinical treatments. This reporting period chemistry efforts have been spent in developing structure activity relationships of a new series of potential JAK2 inhibitors based on novel and patentable phenylpyrimidine and phenylpyrrolopyrimidine scaffolds and PROTAC (proteolysis targeting chimera) molecules. These have been characterized to explore JAK2 inhibition and degradation potential in biochemical and cell line assays. Several of these new compounds are highly potent JAK2 inhibitors. Dr. Schonbrunn, and the structural biology team have solved the X-ray cocrystal structures of one of new inhibitors with the JAK2 kinase domain at a resolution of 2.2 Å, respectively. Both inhibitors bind to the enzyme catalytic site and form two H-bonds with amino acid residue leucine-932 of the hinge region of JAK2. The molecular interactions of the new inhibitors, as revealed by the X-ray structures developed in the project, are facilitating the design of new compounds with improved selectivity for JAK2 through molecular modeling. Importantly the crystal structure reveals the binding mode of the new compounds and the positions where the ubiquitin ligase ligands can be attached via a suitable linker in the design of the PROTACs.

Several of the compounds developed as part of the project both potently and simultaneously inhibit JAK2 and bromodomain-containing protein 4 (BRD4) with potencies comparable or better than current clinical agents. This leads to demonstrated reduction in cell growth of both MPN and multiple myeloma cells. PROTACs based on these inhibitors have been shown to degrade JAK2 or BRD4 in several cell lines. These data are critical for the next step of the project, which will be undertaken in the final funded year, to show compound activity in mouse models of MPNs to provide evidence of the potential clinical impact of the research. A patent application, based on the research outcomes, has been filed this year, “Structural insights into JAK2 inhibition by ruxolitinib, fedratinib, and derivatives thereof,” which seeks to provide protection of intellectual property associated with the new monovalent inhibitors and their PROTAC counterparts. This is important in providing the potential licensing partners (which are being sought through the efforts of the Moffitt Innovation Office) exclusivity to progress a compound to the clinic to benefit patients with MPNs.

Break & Poster Session

Novel metabolic target induces immunogenicity and antitumor synergy with immune checkpoint inhibitor leading to survival benefit

John Copland, PhD
Mayo Clinic Jacksonville

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. The 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, the research team 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. It is now shown 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 Tumor Board (TUBO) model, tumors were completely insensitive to anti-PD1 therapy but when combined with SSI-4, 80% of mice were cured. Thus, the research team discovered that aberrant de novo lipogenesis is linked to tumor immunogenicity, SCD1 inhibitors are immune sensitizing agents and SSI-4 may be used as an adjuvant therapy with other immunotherapies including checkpoint blockade. Together, the results indicate that inhibition of tumorigenic de novo lipogenesis represents a novel approach to enhance T cell-based cancer immunotherapy.

The research team proposes 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 the SCD1 inhibitors. Researchers 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, researchers 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 wherebySSI-4 sensitizes tumors to checkpoint inhibitors, and (3) write a clinical trial. In summary, the research team is developing novel SCD1 inhibitors which are currently not

in development for the treatment of cancer. Researchers predict that these inhibitors will find broad applicability and benefit patient survival, especially in cancer populations where immune checkpoint inhibitors are not effective.

Data-Driven Approaches Targeting Prostate Cancer

Stephan Schurer, PhD for Kelly Burnstein, PhD
University of Miami

Advanced prostate cancer (PC) is particularly challenging to treat because tumors almost always develop the ability to evade drugs, leading to uncontrollable and incurable cancer growth. Tumors acquire "resistance" to drugs by several strategies that vary in different men and can even differ between tumors growing in the same patient. Race and ethnicity also contribute to differences in PC aggressive forms of PC. To combat currently incurable stages of PC most effectively, a precision medicine approach is needed, that is, one in which treatment is tailored specifically to the features of an individual patient's tumor. Fortunately, researchers have huge amounts of available molecular, genetic, and clinical information on PC from a broad variety of different patients. With advanced computer aided (computational) methods, researchers are beginning to identify distinct patterns or "signatures" that occur in drug resistant tumors. The challenge is to exploit these massive amounts of data (also called "big data") in an efficient and logical manner to identify and prioritize new drugs for treating PC. Such data driven approaches, based on disease signatures, have already led to "drug repurposing" in which drugs that are commonly used for one type of disease or condition can be prescribed for treating a different disease including PC. Also, combining two different drugs has proven highly promising for prostate and other cancers, because this approach often results in beneficial clinical responses that are greater than the sum of the two individual drugs (termed synergy). This proposal will leverage the distinct and complementary expertise of two principal investigators: a prostate cancer researcher with a long track record of identifying and testing new experimental PC therapies and a chemist / data scientist who is pioneering the use of big data to identify new drugs and drug combinations (as well as entirely novel methods) to block cancer growth.

The proposed study will integrate collections of big data, including disease and gene signatures that are specific to and representative of a large variety of prostate tumors, with the known responses of over 50 human cancer cells (including PC) to over 1,500 Food and Drug Administration (FDA) approved drugs and compounds in clinical trials plus thousands of additional druglike molecules. A computational algorithm will identify drugs that have a known effect on PC specific gene signatures and are therefore predicted to block growth of tumors with distinct features. The goal is to make highly informed choices about which new drug regimens are appropriate to use on particular tumors. A novel computational platform developed by one of the principal investigators employs computer aided evaluation of tens of millions of different combinations of drugs to predict the precise combinations that will block the growth of different PC tumors. The highest ranked predicted drug combinations will then be tested in mice bearing different human tumors and mimicking the different stages that occur in men with PC, e.g., recurrent tumors, metastatic tumors. The proposed study aims to improve PC treatment outcomes by identifying

patient specific targeted therapies customized to the exact tumor type and the exact stage of tumor development.

Clinical Research & Research Infrastructure

A New Strategy to Increase Proteotoxic Cell Death in Prostate Cancer

Carlos Perez-Stable, PhD
South Florida Veterans Affairs Foundation for Research and Education, Inc.

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. The research team proposes a new strategy that increases proteotoxic stress with cyclophilin + proteasome inhibitors to promote apoptotic cell death in CRPC without toxic side effects. Researchers 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. The 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. 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 six-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. It is proposed 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 the research team is 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.

Clinical Research & Research Infrastructure

Therapeutic Strategies for KEAP1/NRF2 Mutant Lung Cancer

Gina M. DeNicola, PhD
Moffitt Cancer Center/University of South Florida

Targeting the overactivation of cellular growth signaling is now a standard of care for subtypes of advanced non-small cell lung cancer (NSCLC), where adenocarcinomas driven by the estimated glomerular filtration rate (EGFR), or anaplastic lymphoma kinase (ALK) genes can be successfully treated with selective inhibitors. Unfortunately, many patients do not respond to these treatments or relapse following an initial response. Further, despite the presence of overactive growth signals due to alterations in the fibroblast growth factor receptor (FGFR), discoidin domain receptor tyrosine kinase 2 (DDR2) or phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) genes, such targeted agents have yet to demonstrate a clear benefit in patients with squamous cell lung cancer (SCC). Thus, there is dire need to develop new strategies for these patients. Notably, mutations in nuclear factor erythroid 2-related factor 2 (NRF2) and Kelch-like ECH-associated protein (KEAP1) genes have been identified in 29% of SCC tumors and in 18% of adenocarcinomas. These loss of function mutations in KEAP1 and gain of function mutations NRF2 lead to constitutive NRF2 activity. Preclinical studies have suggested mutations in this pathway are associated with poor overall survival and modify the responses to targeted agents, chemotherapy, and radiation therapy. The research team submits that new therapeutics specifically designed against NRF2/KEAP1 will benefit lung cancer patients having mutations in this pathway and that this circuit may play broad roles in treatment responses to all standard treatment modalities used by clinicians.

Despite the prevalence of NRF2/KEAP1 mutations, this pathway is under--investigated in lung cancer. Constitutive NRF2 activity promotes lung cancer growth and the resistance to therapy, but targeted therapies for patients with tumors having NRF2/KEAP1 mutations are lacking. Due to its function within tumor cells, it is difficult to directly inhibit NRF2 directly. This work has shown that NRF2 alters the metabolism of cancer cells and confers druggable metabolic vulnerabilities. Two approaches will be used to selectively target the metabolism of lung cancer cells with high NRF2 activity. The first exploits the addiction of these tumors to NRF2regulated metabolic processes, whereas the second relies on increased levels of select NRF2 targets that can be exploited to provoke cell death. The research team submits that these studies will lay a foundation towards a cure for NRF2/KEAP1mutant NSCLC, which represents a significant patient pool. Further, model systems have been developed harboring NRF2/KEAP1 mutations and are uniquely positioned to use these as platforms to test the response of NRF2/KEAP1 mutant tumors to new therapies. Finally, researchers will leverage the Oncology Research Information Exchange Network (ORIEN), which integrates “big data” and directs data sharing for cancer research and care, to assess how NRF2 affects patient treatment responses. Collectively, the research team will evaluate the feasibility and efficacy of targeting tumor metabolism for treating NRF2/KEAP1 mutant lung cancer and will assess if NRF2/KEAP1 mutation status can be used as a predictor of treatment response and can guide treatment strategy.

Clinical Research & Research Infrastructure

Biobanking for Breast Cancer Prevention and Disparity Research in Florida

Kathleen Egan, ScD
Moffitt Cancer Center/University of South Florida

Breast cancer remains by far the leading cancer diagnosis among Florida women and the second cause of cancer mortality after lung cancer. Despite declining overall death rates, progress has continued to lag in minority and underserved populations. Early detection and prevention are key to reducing breast cancer incidence and eliminating disparity in breast cancer outcomes. In a collaborative project encompassing major academic cancer centers, the team aims to develop a centralized data center and biospecimen infrastructure to support breast cancer prevention research in Florida targeted to screening-aged women. The proposal is to build a comprehensive research infrastructure with standardized collection of epidemiologic data and germline DNA/urine/stool/tissue samples for future breast cancer prevention research. Moffitt Cancer Center is a leader in mammographic breast density determination and Moffitt along with the University of Florida have collaborated over the last several years on studies of the gut microbiome as a novel and modifiable breast cancer risk factor based on mammography patients enrolled at the centers. In this three-year grant, researchers intend to broaden inclusiveness of the study population and specifically to increase representation of minorities and underserved Floridians by initiating similar recruitment and data collection protocols at mammography clinics in Miami and Jacksonville that offer large numbers of Hispanic and African American women, respectively. In this three-year project the aims are:

- Develop methods for outreach and recruitment of minority/underserved women.
- Enroll ~1,600 women undergoing screening mammography at imaging centers affiliated with three project sites.
- Collect detailed lifestyle, medical and reproductive histories via an on-line questionnaire.
- Bank germline oral DNA, urine, stool, and biopsy breast tissue (as applicable) samples.
- Assemble digital imaging data from mammograms and establish a reading center at Moffitt for centralized, standardized evaluation of breast density and novel high-risk mammographic features.
- Explore and lay ground-work for studies of other promising radiographic screening modalities for early breast cancer detection in high-risk women.
- Establish a searchable, on-line database for tracking assembled resources, projects, investigators, contacts, and funding; and
- Implement an administrative frame-work for data use and sample sharing with collaborators and independent researchers throughout the state of Florida.

The project will improve infrastructure/resources in Florida in the designated areas of tissue banking, medical imaging, and health disparities. The research is responsive to four of the seven research priorities of the latest Bankhead-Coley funding initiative, namely, first, prevention in one of five Bankhead-Coley priority cancers (breast); second, screening and early detection with the inherent goal of identifying high-risk subgroups to whom screening protocols may be tailored to achieve reductions in breast cancer mortality; third, health disparity by contributing to understanding of increased breast cancer mortality in African American women via lifestyle factors and genetic/urine/tissue/gut microbiome biomarkers; and fourth, obesity by contributing knowledge on the relationship of obesity to breast cancer disparity and important breast cancer risk factors including breast density and circulating biomarkers.

Clinical Research & Research Infrastructure

Predicting Outcomes of Lung Cancer Therapy Through Explainable Deep Learning

Curtis Lisle, PhD, presenting for Ulas Bagci, PhD
University of Central Florida

Radiation therapies have proven to offer significant treatment advantages to patients presenting with lung cancers. In all types of radiation therapy, the majority of the ionizing energy is focused on the target lesion and its immediate area with lower damage to nearby vital organs. However, some patients still develop complications in the surrounding tissue as a side effect of radiation therapy treatments. This innovative project will conduct a retrospective study across two cohorts of lung cancer patients who received Radiation therapy treatment (including proton therapy). Imaging datasets and clinical documentation created during the treatment process will be used to develop an explainable artificial intelligence (AI) system that functions as an early predictor for treatment outcomes. Many AI systems currently developed today can produce accurate predictions but cannot be used in clinical settings because the reasons for the prediction results are not easily understood, namely black box models, making these systems difficult for regulators to review and approve for clinical use. In contrast, this project will develop an explainable AI system and evaluate its effectiveness using cohorts of patient data curated for this project.

To achieve this overall goal, the team will first collect and process all patient imaging and treatment record documentation using an automated, repeatable process. Then, advanced techniques will generate an explainable and highly accurate system trained to predict clinical outcomes for each individual patient. The predictor will be tested and evaluated against a blind dataset as well as an open dataset with the hypothesis that new algorithms will be more accurate, efficient, and explainable than the conventional radiomics approaches. The blind dataset will be supplied, at no cost, by an existing effort already underway at the Frederick National Laboratory for Cancer Research (FNLCR). The second cohort dataset will be provided by the Radiation Therapy Center at Orlando Health UF Cancer Center in Orlando, FL. All algorithm development will be performed by doctoral students, postdoctoral fellows from the University of Central Florida (UCF), and KnowledgeVis, LLC, a Florida based small business specializing in medical imaging research. Methods development and results validation will be conducted under the supervision of PI Ulas Bagci, PhD of UCF, Co-PI Patrick Kelly MD, PhD of Orlando Health, and Co-PI Curtis Lisle, PhD of KnowledgeVis, LLC.

It is believed that there is a strong collaboration between all Florida based entities is uniquely capable of developing prediction tools for eventual use by clinicians. If successful, this research can improve the outcome of radiation therapy patients suffering with multiple types of lung cancer. It is expected that the outcome of this project to be strong early results, suitable for applying to continue this research with a National Institutes of Health funded study.

Lunch on Your Own - Cafeteria on Site

Casey DeSantis Cancer Research Program, Florida Consortium of National Cancer Institute Centers - Panel Presentation

The Florida Consortium of National Cancer Institute Centers Program is established to enhance the quality and competitiveness of cancer care in this state, further a statewide biomedical research strategy directly responsive to the health needs of Florida's citizens and capitalize on the potential educational opportunities available to its students.

John Cleveland, PhD
Moffitt Cancer Center

Moffitt Cancer Center is one of 53 National Cancer Institute-designated comprehensive cancer centers in the country and the only one based in Florida.

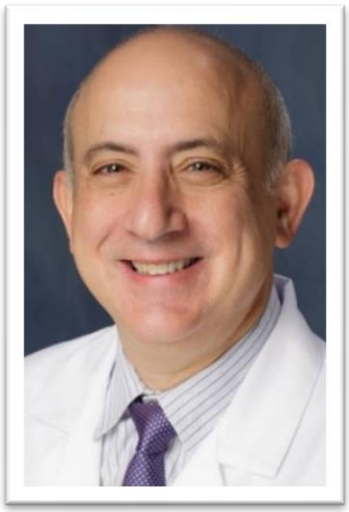
Dr. Cleveland is responsible for elevating Moffitt's research enterprise and reputation for world-class bench-to-bedside science. He will set the strategy and vision for research, overseeing 100 research labs and approximately 175 renowned faculty at Moffitt. He is the principal investigator of Moffitt's Cancer Center Support Grant, which brings in approximately $3 million in NCI funding by delivering transdisciplinary science and driving impact locally, regionally, and beyond.

His research interests include cancer cell checkpoints, cancer cell metabolism, cancer prevention and therapeutics, and the regulation and role of apoptosis and autophagy in the development and maintenance of cancer.

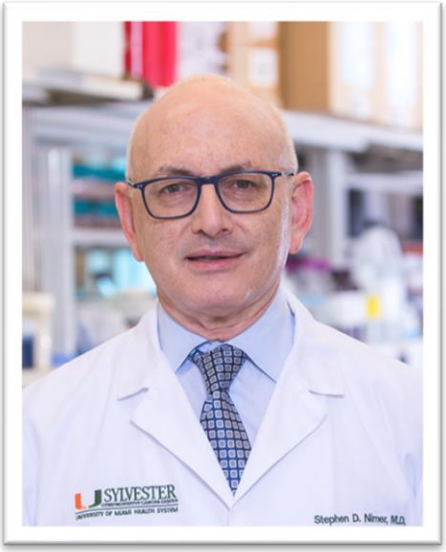
Cleveland is an exceptional scientist and leader, bringing 40 years of experience to this role. He joined Moffitt in 2014 as associate center director of Basic Science. Prior to Moffitt, Cleveland was professor and chair of the Department of Cancer Biology at The Scripps Research Institute. He also held various leadership roles with St. Jude Children's Research Hospital. He began his career working with the NCI, the federal agency charged with leading the National Cancer Program.

Cleveland is a member of the American Association for Cancer Research and the American Society of Hematology. He is a Moffitt Distinguished Scholar and holds the Cortner-Couch Endowed Chair for Cancer Research from the University of South Florida School of Medicine. He earned his bachelor's degree in biology from the University of Maine and his doctorate in immunology and microbiology from Wayne State University School of Medicine.

Jonathan Licht, MD
University of Florida Health Cancer Center



Dr. Licht is the director of the UF Health Cancer Center, holding the Marshall E. Rinker, Sr. Foundation and David B. and Leighan R. Rinker Chair. NCI funded for 30 years, Dr. Licht is also Principal Investigator of a Leukemia and Lymphoma Society (LLS) Specialized Center of Research. Dr. Licht is an Associate Editor of Oncogene and serves on the editorial boards of Cancer Discovery, Cancer Cell, Cancer Research and Clinical Cancer Research. Dr. Licht is chair of the Taskforce for Hematological Malignancies of AACR and is co-chair of the Medical/Scientific Board of the LLS. Dr. Licht has published over 200 articles, reviews and book chapters and has mentored over 40 graduate students and postdoctoral fellows and 20 faculty members. In 2021 Dr. Licht was the winner of the American Society of Hematology Basic Sciences Mentor Award.



Stephen D. Nimer, MD
University of Miami Sylvester Cancer Institute

Dr. Nimer has over 30 years of clinical, research, administrative, and leadership experience in the field of hematology-oncology and cancer. While at Memorial Sloan-Kettering Cancer Center, Dr. Nimer served as the Alfred P. Sloan Chair in Cancer Research, Head of the Division of Hematologic Oncology, Vice Chairman for Faculty Development, and Chief of the Hematology Service. Since coming to the University of Miami-Miller School of Medicine and assuming the Directorship of the Sylvester Comprehensive Cancer Center, Dr. Nimer has focused on developing programs in cancer epigenetics, cancer control, and tumor biology along with establishing facilities and core services that meet the needs of the extraordinary diverse South Florida community. In July 2019, the team became the only NCI designated cancer center in South Florida and the 71st such center in the U.S. As of the end of 2020, Dr. Nimer's team have successfully recruited over 175 cancer physicians and researchers to UM Sylvester, to serve the over six million people who live in the catchment area. The team will continue to pursue The University of Miami Sylvester Cancer Institute's mission of becoming an elite cancer center that makes important contributions to the prevention of and the fight against cancer.

The laboratory has been studying the transcriptional regulation of normal and malignant hematopoiesis for decades, with the aim of understanding how the normal processes of stem cell self-renewal and differentiation are regulated and how these processes are aberrant in the myeloid malignancies. Overall,

the lab has focused on defining genes that contribute to the development and progression of Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) and on identifying novel ways to target hematologic cancers and make them more responsive to treatment. As a physician-scientist, Dr. Nimer has taken care of patients, and conducted clinical trials, for MDS patients and AML patients, for decades. This melding of clinical studies and care, with both basic laboratory and translational studies reflects the fundamental accomplishments of Dr. Nimer's career.

Prevention & Treatment – Abstracts

Multifunctional Nanoparticle for Targeted Combination Therapy of Prostate Cancer

Shanta Dhar, PhD
University of Miami

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. The research team has developed a multifunctional polymer-based nanoparticle (NP) technology 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, researchers 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, researchers 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, adenosine triphosphate (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 the research team to discover a therapeutic modality for treating metastatic prostate cancer, a major unmet clinical need.

Community CARES: A Multilevel Intervention to Increase Colorectal Cancer Screening Adherence in Community Clinics

Clement K. Gwede, PhD
Moffitt Cancer Center/University of South Florida

A leading cause of death in the U.S. is colorectal cancer. It is a significant health concern that affects both men and women and one that the 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, 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. The research team 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 its Community Advisory Board, completes packaging of additional C-CARES components, and finalizes procedures to utilize existing electronic medica 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. The research team thinks that C-CARES Plus will result in greater screening rates at three, 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.

Break & Poster Session

Non-invasive Adiomic Biomarkers to Predict Treatment Response for Immunotherapy of Lung Cancer

Matthew Schabath, PhD
Moffitt Cancer Center/University of South Florida

Cancer immunotherapy has demonstrated durable clinical benefit in 20-50% patients with advanced stage non-small-cell lung cancer. The patterns of IO patient response are complex, including rapid disease progression and acquired resistance. Because of this complexity, there is a pressing challenge to identify predictive biomarkers that can identify patients that are least likely to respond and may experience rapid and lethal outcomes. Though tumor programmed cell death ligand-1 (PD-L1)

expression by immunohistochemistry (IHC) is an approved biomarker, recent published clinical trials demonstrated significant improvements in outcomes regardless of PDL1expression level. Furthermore, tumor mutational burden (TMB) has been shown to be a superior predictor of IO response. However, there are limitations with TMB as tumor specimens need to be sufficient in quantity and quality. Further, tumors are dynamic and accumulate mutations rapidly and laboratory methods to calculate TMB can be timely and expensive. Moreover, tumor-based biomarkers (such as PD-L1 and TMB) are obtained by biopsy with associated morbidities and are subject to sampling bias due to the heterogeneity of the biopsied locations. As such, complimentary biomarkers that are predictive, non-invasive, and measured in a timely fashion would have direct translational implications. Quantitative image-based biomarkers ("radiomics") reflect the underlying pathophysiology and tumor heterogeneity and have many advantages over tissue-based biomarkers, as they can be rapidly calculated from standard-of-care medical images, and they reflect the entire tumor and not just the portion of the tumor that is biopsied as in the case for PD-L1 and TMB. Emerging evidence demonstrates the utility of radiomics as a non-invasive approach to predict lung cancer treatment response of targeted therapy, chemotherapy, and stereotactic radiation therapy. This group has conducted preliminary studies demonstrating that pre-treatment radiomic features combined with clinical data predict rapid disease progression among lung cancer patients treated with IO. Building upon this prior work, the following Specific Aims are to conduct a multi-institutional study to develop and validate radiomic signatures to predict IO treatment response for lung cancer:

Aim 1. Assemble a multi-institutional cohort into a clinical-radiomics database of lung cancer treated with IO. Patients from Moffitt Cancer Center, University of Florida, and James A. Haley Veterans' Hospital will be included. Pre-treatment and follow-up CTs and PET/CTs will be retrieved, and relevant clinical data elements will be obtained. Using an established radiomics pipeline, returns on investment will be identified, segmented, and radiomic features will be extracted.

Aim 2. Build and validate parsimonious models to predict IO treatment response using radiomic and clinical data. In (2.1) the research team will analyze CT radiomics to predict treatment response, in (2.2) researchers will analyze PET/CT radiomics to predict treatment response, and in (2.3) will fuse CT and PET/CT radiomics to predict response. Baseline peritumoral radiomics, intertumoral radiomics, and clinical data will be considered, and machine learning approaches developed by the team will be used to identify parsimonious models that contain the most informative radiomic and clinical covariates to predict patient outcomes. Patients will be randomized into training, test, and validation sets.

CD4+ T effector cells in cancer immunotherapy

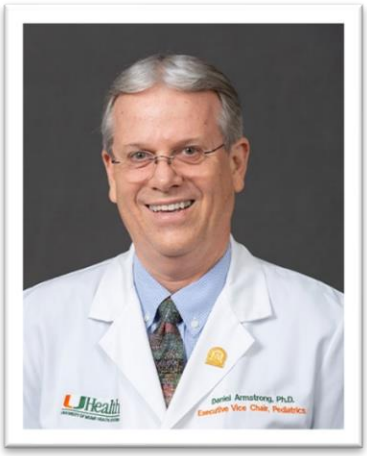
Thomas Malek, PhD
University of Miami

The overall goal of the project is to assess a novel interleukin (IL-2) analog, IL-2/CD25, to enhance tumor immunity and determine its mechanism of action. Past work showed that IL-2/CD25 plus soluble peptide vaccines supported anti-tumor responses in pre-clinical studies in model systems using monoclonal

Prevention & Treatment

CD4+ and CD8+ tumor-reactive T lymphocytes (T cells) and in a more physiological polyclonal setting. During the last year, studies were undertaken to refine the monoclonal T cell model to study the contribution a CD4+ tumor-specific T cells in anti-tumor responses. The first step defined the minimal number of monoclonal T cells that lead to detectable IL-2/CD25-dependent expansion. This step is aimed at establishing a model that would approximate a physiological setting with a low frequency of tumor-reactive T cells as this is necessary to study the interplay between tumor-reactive CD4+ and CD8+ T cells. One unexpected finding is that the CD4+ T cells do not enhance the CD8+ T cells response, which is a critical cell in mediating tumor rejection. Since peptide vaccines are not robust, other vaccine formats will be tested. Initially, a dendritic cell-based tumor peptide vaccine was tested, but these were shown not to be more effective than using soluble peptides. Other experiments examined whether more frequent administration of IL-2/CD25 might increase endogenous tumor-reactive T cells to bypass the vaccine. Under these conditions, IL-2/CD25 supported excellent anti-tumor responses in pre-clinical studies for tumors that were immunogenic. This approach was less effective for non-immunogenic tumors, where a vaccine approach might still be beneficial. Mechanistic studies for immunogenic tumors revealed that IL-2/CD25 monotherapy supported a tumor-microenvironment with enhanced number and function of tumor-reactive T cells while limiting the number of regulatory T cells, which may suppress the anti-tumor response. The potential relevance of these findings is that the anti-tumor activity supported by IL-2/CD25 may eventually become a new treatment for immunogenic cancers, such as melanoma or lung cancer, for patients that fail other therapies. As the IL-2/CD25 fusion protein has been licensed to a large pharmaceutical company, these and other discoveries from this project may impact the lives of Florida resident with cancer.

Closing Remarks



Daniel Armstrong, PhD
Biomedical Research Advisory Council (BRAC) Chair, and Moderator

Poster Session – Discovery Science

Reprograming Tumor Immune Landscape by High Endothelial Venule Formation

Dr. Junko Sawada, DVM, PhD for Masanobu Komatsu, PhD
Johns Hopkins All Children's Hospital

Checkpoint immunotherapies have recently become an extremely promising strategy for cancer treatment because this type of cancer therapy have shown the complete cure of malignant cancers in some patients. An important advantage of immunotherapy is that it causes relatively few significant side effects compared with chemotherapy. To date, however, only a fraction of patients has side effects compared with chemotherapy. To date, however, only a fraction of patients has responded to immunotherapies in lung, breast, and other types of cancer. The success of checkpoint immunotherapy depends on patient's own immune cells, which fight against cancer cells and kill them. In particular, T cells are immune cells primarily responsible for anti-tumor immune activity and have a potential to eradicate cancer cells. However, cancer cells create a type of environment around themselves that inhibits the T cells from penetrating into the tumor interior. If the team can remodel the tumor environment in such a way that T cells can penetrate the tumor, immunotherapies could work for most, if not all, patients. High endothelial venues (HEVs) are a type of blood vessels specialized for recruiting T cells to the site of chronic inflammation. HEVs are also known to form in some cancer patients' tumors and serve as a gateway for T cells to enter the tumor interior and destroy the cancer cells. Consistent with this T cell-recruiting role of HEVs, a high density of HEVs in patients' tumors strongly correlates with· favorable clinical outcomes. These clinical observations suggest that enhanced HEV formation in tumors will create a richly T cell-infiltrated tumor environment and that such a reprograming of immune landscape renders tumors to be highly responsive to checkpoint immunotherapy. The mechanism of HEV formation is poorly understood at present. The new findings from the laboratory suggest that a Ras homolog protein R-Ras, which is expressed in the inner lining of tumor blood vessels, promotes the formation of HEVs in patients' tumors. Through comprehensive genetic analyses of HEVs, researchers also identified additional "signature" molecules of HEVs that are thought to be important for the regulation of HEVs. Researchers hypothesize that the manipulation of these molecules would lead to abundant T cell infiltration and greater anti-tumor T cell immunity via increased HEV formation. In this proposal, the research team will investigate these HEV signature molecules in human lung cancer and other types of cancer. The research team will establish correlations between their expression, abundance of HEVs, infiltrating immune cell profile, Th1/Th2 cytokine profile, and the retrospective clinical outcomes of each corresponding patient. In the short-term, the successful outcome of this study will determine how tumor vasculature may be targeted to generate highly inflammatory tumor environment that is sensitive to checkpoint immunotherapies. The current low response rate to checkpoint immunotherapy is one of the most important clinical challenges in cancer treatment. In the long-term, the new understanding gained from this study will allow the research team to explore novel strategies to create immune stimulatory environment in patients' tumors, thereby making the non-responder patients to be responders of the immunotherapies. If this approach is found to be feasible and effective, there will be a direct and significant impact of such a finding to the care of cancer patients.

Lipid-nanoparticle vaccines targeting metastatic lung cancer from osteosarcoma

Elias Sayour, MD, PhD
University of Florida

Despite multimodality approaches for osteosarcoma (OS), including chemotherapy and limb amputation, a significant percentage of children/adolescents succumb to disease due to the presence of lung metastasis; these outcomes necessitate development of novel targeted therapeutics. Immunotherapy promises to redirect the host immune system against OS but remains limited by the dearth of antigen specific targets and the immunosuppressive tumor microenvironment. To circumvent the lack of OS specific targets and overcome intertumoral immunosuppression, the group has developed a novel treatment platform that consists of clinically translatable nanoparticles (NPs) combined with personalized tumor derived mRNA. These ribonucleic acid polymerases (RNANPs) can simultaneously function as both a vaccine and an innate immunomodulating agent to reprogram OS mediated immunosuppression into an immune activated milieu.

The research has shown that intravenous administration of tumor mRNA loaded NPs transfect antigen presenting cells and lead to an activated T cell response for induction of antitumor immunity in preclinical models. In contrast to other vaccine formulations, RNANPs recruit multiple arms of the immune system (i.e., innate and adaptive), and remodel the systemic/intratumoral immune milieu, which remain potent barriers for vaccine, cellular, and checkpoint inhibiting immunotherapies. In murine pulmonary OS models, RNANPs induce robust antitumor efficacy (around 87.5% long-term survivor benefit) and mediate synergistic activity in settings where immune checkpoint inhibitors (i.e., antiPDL1 therapy) do not confer therapeutic benefit. Drs. Sayour and Heldermon will explore mechanisms of treatment resistance in syngeneic immunocompetent murine models for metastatic OS (MOSJ and K7M2). They will then use the nanoparticle delivery strategy to target identified mechanisms before pursuing a translational canine study exploring the safety and activity of combination RNANPs in canines with OS (nearly 100% homologous to the human form of the disease).

Tumor and Stromal Targeted Oncolytic Virus Based Biotherapies for Colorectal Cancer

Jaime Merchan, MD
University of Miami

Despite major advances in the therapeutic landscape in advanced colorectal cancer (CRC), the majority of patients still succumb from progressive disease. Advanced CRC rapidly develops resistance to standard chemo and targeted therapies, and the great majority of cases do not respond to checkpoint inhibitors alone. Therefore, development of novel biotherapies able to overcome resistance to currently available CRC agents is an urgent medical need. Oncolytic viruses (OVs) are promising biological antitumor agents that offer an advantage over conventional oncology drugs, because they can be genetically engineered to target, replicate in, and kill tumor cells. In addition, they may also act as immunomodulatory agents. Among the different OV platforms currently being developed, the oncolytic

measles virus (MV) is a promising one, as it has shown safety and antitumor activity in vitro, in vivo and in early phase clinical trials. There are several obstacles, however, limiting the efficacy of systemically administered OVs. They include inadequate viral entry due to the tumor stromal barrier, limited viral cytotoxicity due to decreased tumor viral replication, and short lived viral induced antitumor immunity. The long-term goals are to overcome this barrier by developing stromal retargeted oncolytic measles viruses and to improve viral oncolysis by combination novel antitumor agents. The research team generated preliminary data showing that novel oncolytic MVs fully retargeted against human or murine urokinase receptors has significant antitumor effects in vitro and in vivo models of colorectal cancer by targeting both the tumor and importantly, the stromal cells compartments of the tumor. While significant antitumor effects were observed, complete responses were not observed. In preliminary studies, researchers found that combination of oncolytic MVs and the novel agent triptolide lead to significant increase in tumor cytotoxicity in vitro, probably by enhancing viral replication and inducing increased tumor cell apoptosis. This is a novel, promising combination that may significantly improve antitumor responses in colon and other cancers. The objectives of the application are to further characterize the mechanisms by which OV stromal targeting enhances the virus' overall oncolytic effects, and to further evaluate the effects and molecular mechanisms of the virus triptolide combination in models of colorectal cancer. Researchers propose to achieve these objectives by pursuing three aims: 1) to characterize the mechanisms of tumor-stromal interactions in colorectal cancer models; This will be pursued by characterization and molecular analysis of stromal cell components before and after treatment in vitro and in vivo. 2) To test the in vivo efficacy of tumor, stromal or dual targeted oncolytic MVs in combination with minnelide in CRC xenografts and syngeneic models of CRC, and 3) To characterize the in vivo effects of MV on the immune stroma and their modulation by minnelide, checkpoint inhibitors or both in syngeneic CRC models. The above studies will bring significant new knowledge in the field of stromal targeted oncolytic viruses and has the potential to bring a novel new combination strategy for the treatment of this fatal disease. The extensive preliminary data, as well as the resources, experience, and expertise the research team has gained in the last eight years in the OV field provide assurance that the research team will successfully achieve the above aims and objectives of the application.

Etiology, and Mortality for Highly Fatal Cancers in Diverse Florida; Unique Impact on African Americans, Afro-Caribbeans, Cubans, Puerto Ricans, and Other Hispanics

Paulo S. Pinheiro, PhD
University of Miami

Lung cancer is the leading cause of cancer death and Liver cancer is the fastest growing cancer, both in the US and the Sunshine state of Florida, (population 21 million) where combined they account for over 13,000 deaths each year. Unfortunately, survival prospects are dismal for both diseases. Currently only 18% of liver cancer patients and 17% of lung cancer patients survive five years. Lung cancer mortality is highest among African Americans while Liver cancer disproportionately affects all non-White minorities. However, the rich racial/ethnic diversity in Florida has yet to be leveraged to explore their underlying etiologies and clinical and biological characteristics impacting mortality. To address these disparities,

knowledge about the specific risk factors and etiologies driving these cancers for each distinct population in Florida needs to be clarified so that actionable public health and clinical interventions can take place. Researchers propose to study the lung and liver cancer experience for twelve distinct racial/ethnic groups in Florida, beginning with the typically studied major groups, White, Black, and Hispanic, but also distinct subgroups with sizable populations in Florida, including African American (US Born), Afro-Caribbean, Cuban, Puerto Rican, Mexican, Dominican, Central American, and South American. This knowledge will enable the development of specific approaches for high-risk groups, including tobacco control, and access to curative treatment for lung cancer, and screening underlying liver disease and for hepatitis B and/or C for liver cancer. The first aim is to determine the incidence and survival of lung cancer for each race/ethnicity and to study and identify the clinical, biological, and social determinants of lung cancer survival for all twelve populations. Sub analyses will include an in-depth assessment of lung cancers among nonsmokers, rarely studied but with a heavier impact among racial/ethnic minorities and women, as well as the identification of any disparities in the receipt of surgical treatment for localized NSCLC (non-small cell lung carcinoma) tumors, most amenable to cure. The second aim is to determine cause-specific liver cancer incidence and survival, for both major types of liver cancers, HCC (hepatocellular carcinoma) and ICC (intrahepatic cholangiocarcinoma), examining the known etiologies of liver cancer: hepatis C, hepatis B, alcohol liver disease, NAFLD, diabetes, and rarer genetic, autoimmune/inflammatory, and biliary conditions. Special emphasis will be placed on the patterns among baby boomers, known to have higher HCV prevalence and a higher liver cancer burden. Florida's hospital discharge data, viral hepatitis and mortality data will be linked with cancer registry data to provide unique etiology specific information for a large, representative statewide cohort of Hispanic and Black minority subgroups, never studied with this level of detail anywhere else in the US. Over 200,000 lung and 22,000 liver cancer cases over the course of thirteen years (20052017) have been preliminarily identified using the Florida Cancer Data System. This proposal will use unique data and innovative multisource linkages to produce entirely novel information about Florida's diverse cancer profile. Community outreach to disseminate the results will provide invaluable information for both public health and clinical practitioners, tasked with combatting the scourge of these two deadly cancers.

Ursolic Acid as a Countermeasure to Cancer Cachexia

Andrew Judge, PhD
University of Florida

Cachexia is a devastating catabolic condition characterized by the progressive loss of skeletal muscle mass and body weight which affects up to 80% of patients with cancer. The loss of muscle mass contributes to functional deterioration of both locomotor and respiratory muscles 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 responsible for up to 30% of all cancer related deaths. Unfortunately, there is currently no medical therapy for cachexia, which is an enormous unmet need to improve quality of life and enhance survival of cancer patients. In 2011, ursolic acid was discovered to induce an mRNA expression signature which negatively correlated with the mRNA

expression signature of atrophying human skeletal muscle in response to spinal cord injury and fasting, suggesting that ursolic acid might counter muscle atrophy. Ursolic acid is a natural compound derived from several edible herbs and fruits, including apples. Since 2011, ursolic acid has been shown to reduce muscle atrophy in rodent models of muscle disuse, fasting, spinal cord injury, chronic kidney disease, and aging but has never been tested as a countermeasure to cancer cachexia. However, preliminary data collected for this proposal suggest that ursolic acid can reduce muscle and fat wasting (cachexia) in mice injected with colon 26 adenocarcinoma cells. Based on this exciting preliminary finding, coupled with the favorable safety profile of ursolic acid, with an oral lethal dose 50 (LD50)> 8,000 mg/kg and an intraperitoneal LD50> 600 mg/kg in mice, researchers propose to conduct a pre-clinical trial of ursolic acid in multiple mouse models of cancer cachexia. To do this, the team will inject mice with murine or human colon, lung, breast, or pancreatic cancer cells and, once tumors are palpable, treat mice with ursolic acid or vehicle, with or without cancer-specific chemotherapy. With completion of this pre-clinical trial, the research team will have established the extent to which ursolic acid can attenuate cachexia, and improve muscle and respiratory function, in response to four different cancers using murine and human cancer cells in mice which are naïve to, or treated with, chemotherapy. A positive outcome from this work could lead to a subsequent clinical trial for ursolic acid to impede cachexia and improve functional outcomes in cancer patients.

Discovery of Marine Natural Products Active Against Triple Negative Breast Cancers Using 3-D -spherioid Cultures: An In Vivo Relevant Assay Platform

Esther Guzman, PhD
Florida Atlantic University

The research team are investigating the use of marine natural compounds to treat triple negative breast cancers. Triple negative breast cancers, which represent about 12% of breast cancers diagnosed in the United States, can be very aggressive and easily spread to other organs, particularly the brain and the lungs. They are more likely to recur than other breast cancers and are classified as high-grade tumors because of the minimal resemblance these cancer cells have to normal cells.

The objective of this research is to identify compounds from the extensive marine natural products library at Florida Atlantic University's Harbor Branch Oceanographic Institute that can induce programmed cell death (apoptosis) in triple negative breast cancer cells grown as spheroids. Cells grown as spheroids more closely mimic tumors, and, therefore, are expected to be more easily translated to the clinic. The hope is that these clinically active compounds will provide more effective treatment options for triple negative breast cancers, with less side effects and greater survival rates. The five-year survival rate for triple negative breast cancers is 77% compared to 93% for other breast cancer types.

The research team will use a multi-parametric cell-based assay that uses high-content imaging to measure the cell number, induction of apoptosis and viability in two triple negative breast cancer cell lines grown as spheroids. So far, the research team has purchased both cell lines, created frozen stocks and determined the fractions that will be tested. It also has obtained quotes for several of the reagents which are in the process of being purchased. Additionally, researchers have established an account with

MD Anderson Cancer Center so they can send samples to be analyzed by the center's Reverse Phase Protein Array (RPPA) Core Facility.

Proteogenomics of Metastatic Heterogeneity and Therapeutic Resistance in Lung Cancer

John Koomen, PhD
Moffitt Cancer Center

Lung cancer has limited treatment options for advanced, recurrent, or metastatic disease. Frontline treatment has traditionally consisted of chemotherapy, but targeted drugs (e.g., estimated glomerular filtration rate (EGFR), or anaplastic lymphoma kinase (ALK)) and immunotherapy are showing significant impact in improved patient outcomes. However, no strategy is currently curative, so the research team must study advanced lung cancers resistant to these therapies to develop molecular classifiers of response and resistance as well as design novel treatment strategies. The first step is to elucidate the biology of drug resistant lung tumors. To support this goal, the research team consents patients for rapid tissue donation after autopsy. Multiple metastatic lesions from nine patients that died from their cancer (three small cell lung cancer, six adenocarcinoma) have been collected and annotated with clinical data, including serial radiology studies documenting the response or resistance to therapy of each tumor site. The diagnoses and treatment regimens for three example patients are: a small cell lung cancer patient treated with chemotherapy, a Kirsten rat sarcoma virus (KRAS) mutant adenocarcinoma patient treated with immunotherapy and targeted therapy, and an ALK-positive adenocarcinoma patient treated with chemotherapy, immunotherapy, and ALK inhibitors. The team will explore changes associated with metastasis and address the hypothesis that tumor drivers include sequencing to detect mutations and fusions, gene expression measurements from RNASeq, expression proteomics, and quantification of protein biomarker panels. Mutation patterns from genomics will define the sequence of spread throughout the body to establish the natural history of the disease. To define specific adaptations to metastatic niches and microenvironmental support mechanisms in each organ site, the research team will compare proteogenomic changes between primary lung tumors, local lung metastases, and metastases to other organs. Furthermore, the research team will test the hypothesis that response or resistance to each type of treatment is determined by the adaptations and microenvironment of each metastatic tumor. The research team will focus initially on:

1) Conventional chemotherapy DNA damage response elements and detoxifying enzymes
2) Immunotherapy tumor mutation burden, infiltrating immune cells, immune checkpoint proteins and ligands.
3) Targeted Therapy – kinases

Also, bioinformatics approaches will identify changes in genes and proteins relevant to resistance to each type of treatment to improve understanding of evasion of therapy and the reasons why these tumors were fatal to the patient. The primary endpoint of this study is to increase knowledge of metastatic and drug resistant lung tumors and confirm these candidate biomarkers with pathology follow up experiments; secondary goals include gene/protein correlations, biomarker development with proteomics or immunohistochemistry, and targetable vulnerabilities. In summary, the team will expect

to improve knowledge of lung cancer, particularly emphasizing signaling, heterogeneity of different metastatic lesions growing in the same patient, and phenotypes of drug resistant tumors to define novel vulnerabilities that can be assessed in the patient and targeted with novel treatment strategies for metastatic tumors with companion biomarkers that predict their success.

Poster Session – Prevention & Treatment

Characterizing oncogenic function of ITCH in melanoma

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The combination of BRAF and MEK targeted therapies with antiPD1 immunotherapy is now the standard of care for patients of BRAF-mutated melanoma. For BRAF wildtype melanoma and other types of solid tumors, however, MEK inhibitor monotherapy often shows little advantage over chemotherapies. Thus, new strategies for targeted therapy combination are urgently needed. The itchy E3 ubiquitin protein ligase (ITCH) gene has been well characterized as a key molecule in immune cells. Itch knockout mice develop autoimmune phenotypes through several mechanisms modulating both T cell and B cell functions, and the gene was therefore named after the itchy phenotype. On the other hand, roles of ITCH in tumorigenesis, especially in the in vivo settings, are less explored. The research team has recently uncovered that ITCH promotes BRAF activation in response to proinflammatory cytokines in BRAF wildtype melanoma cells. ITCH deficiency led to a drastic reduction of viability in BRAF wildtype melanoma cells both in culture and in the mice. Interestingly, BRAF wildtype mouse melanoma cells developed smaller tumors in Itch knockout mice. Based on recently published as well as preliminary data, researchers hypothesize that that in BRAF wildtype melanoma cells, ITCH is therapeutic vulnerability in both melanoma cells and the tumor immune microenvironment. In melanoma cells, proinflammatory cytokines activate the JNK ITCH pathway to sustain oncogenic pathways including mitogen-activated protein kinases (MAPK) and melanocyte inducing transcription factor (MITF); Activation of ITCH in immune cells, on the other hand, fosters an immunosuppressive tumor microenvironment. Hence targeting ITCH could be a novel strategy to kill two birds with one stone. Inhibiting ITCH function may also sensitizes MEK and immune checkpoint inhibitors in BRAF wildtype melanomas. To test the hypothesis, the team will aim to: 1) define mechanisms by which ITCH facilitates melanoma cell proliferation and migration; 2) determine if activation of ITCH in melanoma cells promotes tumorigenesis; 3) assess the oncogenic roles of ITCH in melanoma cell survival and immune evasion in vivo. The completion of these studies will provide a strong basis for the long-term goals to develop small molecules specifically inhibiting ITCH, to assess if targeting ITCH is also an effective strategy in other RAF activated solid tumors, and to translate these discoveries into new investigator initiated clinical trials.

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