Fall 2021
Developmental Research Awards

Tier 1 – Clinical/Translational

PI: Samuel Rubinstein, MD, Assistant Professor, Medicine

Project Title: Risk of Acute Lymphoblastic Leukemia in Patients with Multiple Myeloma on Immunomodulatory Drugs

Abstract
Multiple myeloma is the second most common hematologic malignancy in the United States and is more common among black Americans. Immunomodulatory drugs (IMiDs) such as lenalidomide and pomalidomide have become a cornerstone of therapy for multiple myeloma but cases of secondary malignancies are an area of concern. IMiDs are thought to work by causing proteasome-mediated degradation of the B cell-specific transcription factors, IKZF1 and IKZF3 resulting in subsequent plasma cell death. At our institution we have identified five cases of patients with multiple myeloma that were treated with IMiDs and subsequently developed acute lymphoblastic leukemia (ALL). Myeloma patients are also known to make up a disproportionately large segment of therapy-related ALL. The issue of secondary malignancies is especially relevant for IMiDs as 1) patients with myeloma will commonly be maintained on IMiDs for years, developing a high lifetime exposure, 2) there are many treatment options other than IMiDs for myeloma patients, and 3) IMiDs are being used in clinical trials for benign hematologic conditions, specifically hereditary hemorrhagic telangiectasia ("HHT"). While we know of multiple tertiary care institutions that are investigating the genetic mechanisms underpinning the development of ALL, a cancer of early B cells, while treating myeloma, a cancer of terminally differentiated B cells, none to our knowledge are pursuing the population-level studies to confirm IMiD exposure as a risk factor for the development of ALL in patients with multiple myeloma. Here we propose using the SEER-Medicare database to demonstrate correlation between lenalidomide and pomalidomide exposures in myeloma patients to the development of therapy-related ALL.

Tier 1 – Clinical/Translational

PI: Nadja Vielot, PhD, Assistant Professor, Family Medicine

Project Title: Identification of Methylation Biomarkers to Improve the Management of Low-grade Cervical Lesions Detected During Cervical Cancer Screening

Abstract
Background: Approximately 3 million Pap tests return abnormal results in the United States annually, most of which are low-grade squamous intraepithelial lesions (LSIL). It is difficult to predict which LSIL will progress to more severe disease, so LSIL patients are regularly subject to colposcopy and biopsy for definitive histologic diagnosis. The American Society for Colposcopy and Cervical Pathology supports novel technologies to reduce the burden of cervical cancer screening on patients and the healthcare system. Cervical DNA methylation patterns are promising biomarkers to improve characterization and prognostication of LSIL. **Objective:** To assess the utility of cervical methylation markers to characterize and predict outcomes of screening-detected LSIL. **Methods:** Leveraging existing clinical data and cervical samples from the Cervical Intraepithelial Neoplasia Cohort Study—a prospective cohort of women with abnormal Pap tests in North Carolina—we will test LSIL samples with the Illumina HumanMethylation EPIC BeadChip array to assess DNA methylation levels at >850,000 sites. Project

Specific Aims are to: 1) assess associations between altered methylation levels and histologic diagnosis of low-grade cervical intraepithelial neoplasia or more severe (CIN1+) among LSIL cases (cross-sectional); and 2) assess associations between altered methylation levels and LSIL persistence or progression (prospective). We hypothesize that methylation is positively associated with baseline CIN1+ (Aim 1) and with higher risk of persistence/progression (Aim 2). **Potential impact:** This study explores medical technologies to improve risk stratification and decision-making for screening-detected LSIL. Promising methylation markers can be translated into commercial biomarker assays for routine screening, improving capacity for cervical cancer prevention.

Tier 1 – Clinical/Translational

PI: Jen Jen Yeh, MD, Professor, Surgery and Pharmacology

Project Title: Liquid Biopsy for Pancreatic Cancer Subtyping

Abstract

The goal of this proposal is to develop a non-invasive, liquid biopsy assay to diagnose pancreatic ductal adenocarcinoma (PDAC) molecular subtypes. PDAC is an aggressive disease, often presents at an advanced stage and has minimal response to treatment, all of which contribute to a 5-year survival rate of less than 10%.1 Our group identified PDAC molecular subtypes (basal and classical), which correlate with prognosis and treatment response. “Precision medicine,” or tailoring treatment selection based on their tumor molecular subtype, is an area of current activity and interest, showing potential of therapeutic and clinical benefit. With Dr. Naim Rashid, we developed a single sample classifier that is now CLIA approved and is being tested in a clinical trial as a way to select first-line treatment for PDAC patients. A significant challenge that remains is that current methods for tumor subtyping are dependent on invasive tumor biopsies and thus limited to high volume institutions experienced in endoscopic ultrasound guided biopsies. We have identified significant correlation of methylation sites and our tumor subtypes. Selected methylated cfDNA assays have already been CLIA approved. This proposal will use methylation markers that correspond with basal and classical subtypes and create a minimally invasive, blood-based assay that can be used clinically to classify the molecular subtype of patients’ PDAC tumors help physicians select treatment for PDAC patients without the need for tissue biopsy.

Tier 1 – Population Science

PI: Rebecca Fry, PhD, Carol Remmer Angle Distinguished Professor and Professor, Environmental Sciences and Engineering

Project Title: Toxic Metals in Private Well Drinking Water and Cancer Prevalence

Abstract

There is a pressing knowledge gap regarding the relationship between exposure to toxic metals via well water and cancer risk in North Carolina (NC). Well water quality remains unregulated, despite over 2.3 million people using private wells in NC, presenting a significant route of exposure to toxic metals including inorganic arsenic and uranium. It is well-documented that access to regulated public water supply is influenced by structural environmental racism and ability to ensure the quality of one’s well water is affected by socioeconomic status. Many metals found in well water, specifically inorganic arsenic and uranium, have been identified as carcinogens in humans. Preliminary analyses highlight that 6 and 9% of private drinking wells in NC exceed federal standards of 10 and 30 ppb for inorganic arsenic and uranium, respectively. Moreover, the highest observed levels of inorganic arsenic and uranium were

806 ppb and 1,970 ppb, respectively - exposure levels that drastically increase cancer risk. Despite this, no systems currently exist to address human health risks posed by elevated concentrations of these carcinogens in NC. This study will test the hypotheses that levels of inorganic arsenic and uranium in private drinking wells are associated with social vulnerability and increased risk of bladder and thyroid cancer, respectively. Outcomes from this study include: (i) the examination of racial and/or income disparities in inorganic arsenic and uranium levels in private drinking well water in NC; (ii) determination of the association between inorganic arsenic and bladder cancer; (iii) determination of the association between uranium and thyroid cancer.

Tier 1 – Population Science

PI: Chemtai Mungo, MD, MPH, Assistant Professor, Obstetrics and Gynecology

Project Title: High-risk human papillomavirus (hrHPV) persistence following thermal ablation among HIV-positive and HIV-negative women in a low-resource setting and impact on cervical pre-cancer treatment outcomes

Abstract
Low- and middle-income countries (LMICs) account for a disproportionate burden of cervical cancer cases globally due to the lack of human papillomavirus (HPV) vaccination programs and accessible precancer treatment. Women living with HIV (WLWH), a majority of whom live in LMICs, are at increased risk of cervical cancer due to higher incidence and persistence of HPV infection, the causative agent. In 2019, the World Health Organization (WHO) launched a 90/70/90 strategy for global cervical cancer elimination, calling for 90% HPV vaccination, 70% cervical cancer screening coverage, and treatment of 90% of cervical precancer detected at the screening by 2030. Current precancer treatment programs in LMICs primarily rely on ablation, and increasingly, thermal ablation with easy to use, portable, battery-powered devices that can be performed by nonphysician health workers and hence are highly scalable. However, despite a WHO endorsement, data on the efficacy of thermal ablation for treatment of precancerous lesions among WLWH, as well as predictors of treatment failure, are lacking. Prior studies have demonstrated a clear link between persistent infection with high-risk HPV (hrHPV) strains following treatment, particularly HPV 16 and HPV18, and precancer treatment failure. However, due to lack of routinely accessible HPV testing in LMICs, little is known about the frequency of hrHPV persistence following thermal ablation and its role in driving precancer treatment failure among WLWH. This study will leverage an ongoing USAID-funded trial in Malawi performing hrHPV-screening coupled with thermal ablation treatment among HIV-positive and HIV-negative women in Malawi to fill this important knowledge gap.

Tier 1 – Population Science

PI: Hung-Jui (Ray) Tan, MD, MSHPH, Assistant Professor, Medicine

Project Title: Building virtual peer navigation to support testis cancer care and survivorship

Abstract
Background: Testis cancer is the most common cancer among young adult men and the 7th most common among male cancer survivors in the US. Though highly curable, patients face multiple survivorship issues related to treatment-related morbidity, surveillance, and work/life challenges. Given the demographics, online support may be a potential strategy to help testis cancer survivors. However,

the care and survivorship needs of this population remain poorly defined. **Objective and Specific** Aims: Taking a patient-engaged approach, this study seeks to build the foundation for virtual peer navigation and support for patients with testis cancer and includes two specific aims: 1) To define the care and survivorship needs among men treated for testis cancer; and 2) To assess the content quality of online resources for testis cancer from the patient and provider perspectives. **Study Plan:** In Aim 1 with guidance from our patient advisory board, we will leverage UNC's Health Registry/Cancer Survivorship Cohort to conduct a convergent mixed methods study where we analyze survivorship surveys and interview cohort participants to characterize their care and survivorship needs. In Aim 2, the research team and patient advisory board will rate online support resources for testis cancer on whether they address key domains of survivorship using a validated instrument and a modified Delphi procedure, so both perspectives are captured. **Significance and Relevance:** This research will support community building and patient engagement and generate preliminary data needed to pursue extramural funding for larger-scale initiatives to improve quality and survivorship for testis cancer patients in North Carolina.

Tier 2 – Basic Science

PI: David Drewry, PhD, Associate Professor, Chemical Biology and Medicinal Chemistry

Project Title: Covalent ligands of the transcription factor brachyury for chordoma and breast cancer

Abstract
The transcription factor brachyury, encoded by the gene TBXT, is a key driver and a master regulator of the rare cancer chordoma. Mounting evidence indicates that brachyury plays important oncogenic roles in other cancers as well, including breast cancer where its expression predicts poor outcome. Brachyury is a key developmental protein that is turned off after playing its role in notochord development, therefore is minimally expressed in adult tissues making it an attractive therapeutic target. However, transcription factors are notoriously difficult to inhibit as they lack better defined target sites found in many enzymes or receptors. We have identified a ligandable binding site in brachyury that contains a reactive cysteine. We have discovered covalent compounds that bind to this cysteine, and in chordoma cells and triple negative breast cancer cells our compounds lead to decreased expression of brachyury. Additionally, for this Lineberger Stimulus proposal, we explore key genomic and oncogenic regulatory mechanisms that are driven by brachyury in cells derived from triple negative breast cancer, an extremely difficult to treat disease. We hypothesize that covalent ligands of brachyury will lead to decreased levels of brachyury expression, and this brachyury depletion will inhibit key oncogenic mechanisms in cancers with aberrant brachyury expression. For this project we will optimize our lead molecules and use both compounds and cell lines with inducible brachyury knockdown to evaluate the effects of brachyury modulation on key oncogenic processes in disease-relevant cellular systems for both chordoma and triple negative breast cancer lines.

Tier 2 – Basic Science

PI: Melanie Simpson, PhD, Department Head, Molecular and Structural Biochemistry, N.C. State University

Project Title: Covalent ligands of the transcription factor brachyury for chordoma and breast cancer

Abstract

Recurrence of prostate cancer following androgen deprivation therapy (ADT) has few treatment options and a high mortality rate. Castration resistant prostate cancer (CRPC) is hallmarked by aggressive tumor and metastatic growth that is no longer dependent on circulating testosterone. Prostate cells control potency and availability of androgens in part by inactivating them through the glucuronidation pathway.

We have implicated UDP-glucose dehydrogenase (UGDH), which provides the UDP-glucuronate precursor for glucuronidation, as a critical regulator of prostate tumor androgen response, and found that UGDH acts as a sensor that directs precursors to glucuronidation in response to metabolic conditions. We recently implicated a novel kinase as a cellular regulator of UGDH activity through phosphorylation of a serine located at the UGDH subunit contact interface critical for its normal function. The increased understanding of mechanisms controlling the cellular prioritization of UGDH enzymatic activity provides a strong rationale for its potential use as a therapeutic target in prostate cancer. We propose two aims: 1) Determine the efficacy of kinase-UGDH combined inhibition in the control of tumor cell androgen dependence and therapeutic response. We will use a peptide inhibitor of UGDH identified through phage display as proof of concept to demonstrate anti-proliferative effects of pharmacological UGDH targeting in vitro. 2) Use a high throughput approach to identify small molecule lead compounds for selective inhibition of UGDH. The UGDH-binding peptide will be used as a probe to inform small molecule inhibitor discovery by computational and biochemical screening methods. Manipulation ofUGDH activity in combination with inhibition of its putative regulatory kinase will support use of the kinase-UGDH "axis" as a selective therapeutic target.

Tier 2 – Clinical/Translational

PI: Nikia Laurie, PhD, Associate Director, Julius L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University

Project Title: Obesity, Disparities, Epigenetics and Insulin/IGF-1 and Wnt/beta-catenin Signaling in Endometrial Cancer

Abstract

Non-Hispanic Black (NHB) women suffer a 55% higher mortality from EC than non-Hispanic white (NHW) women. This disparity may reflect a combination of a higher risk of more lethal tumor molecular subtypes and greater rates of obesity/diabetes in NHB women. We interrogated the Cancer Genome Atlas (TCGA) and uncovered differences in the obesity-related insulin/IGF-1 pathway and DNA methylation in ECs from NHB/NHW women. We also found that increased expression of a key member of the Wnt pathway, catenin beta-1 (CTNNB1), was associated with decreased EC survival. In September 2020, we initiated the Carolina Endometrial Cancer Study (CECS), a prospective population-based study, to better understand EC disparities. Given the higher obesity/diabetes rates in NHB women, we hypothesize that alterations in obesity related pathways, insulin/IGF-1 and Wnt/β-catenin, combined with differences in DNA methylation, drive racial disparities in EC. In Aim 1, we will define alterations in the insulin/IGF-1 and Wnt/β-catenin pathways in ECs from NHB vs NHW women via CECS by utilizing DNA profiling and RNA sequencing analysis. In Aim 2, we will determine the impact of obesity on insulin/IGF-1 and Wnt/β-catenin pathway signaling in pre-clinical patient-derived xenograft (PDX) mouse models of EC. In Aim 3, we will identify differential sites of DNA methylation in ECs from NHB and NHW women using samples from CECS and our PDX models. This study will be the first to use a population-based platform (CECS) and multifaceted approaches to investigate insulin/IGF-1, Wnt/β-catenin signaling and epigenetic changes in the underlying biology of NHB disparities in obesity-driven ECs.