Tier 1: Basic Science

PI: Xian Chen, PhD, associate professor, Department of Biochemistry & Biophysics

Project Title: Deciphering non-canonical functions of the histone methylase G9a in TNBC carcinogenesis and therapy

Abstract
Effective therapeutic options for triple-negative breast cancer (TNBC), the most metastatic, aggressive form of the disease, are severely lacking because the molecular mechanisms that contribute to TNBC tumorigenesis are poorly understood. Current, largely incomplete models of carcinogenesis fail to explain exactly how oncogene mRNAs are selectively translated. Recent evidence indicates that METTL3, an N6- methyladenosine (m^6A) methylase, mediates oncoprotein translation. However, *nothing is known about the proximal factors that determine this pro-tumorigenic function of METTL3*. Using our chromatin-activity-based chemoproteomics, a clinical-compatible mass spectrometry (MS) technology, we discovered *in tissues of poor- prognosis TNBC patients* enhanced association of the histone methyltransferase G9a with METTL3 and, particularly, with translation initiation proteins such as eIF3. Further, we discovered that G9a methylates METTL3 and substitution of G9a-target lysines altered METTL3 binding to eIF3 that is otherwise critical for pro- tumorigenic METTL3-mediated translation. We hypothesize that, via TNBC-specific interaction with METTL3, constitutively active G9a functions in a non-canonical (non-histone modification) manner to promote translation of TNBC-driving oncoproteins. We will test this hypothesis as follows: 1) Determine the molecular mechanism by which G9a regulates METTL3-mediated translation, and 2) Define the G9a-dependent function of METTL3 in TNBC carcinogenesis. Because m^6A is the most abundant mRNA modification in 'epitranscriptional' regulation, we will delineate new wide-spread mechanisms that underlie non-canonical functions of G9a in m^6A epitranscriptional regulation, a heretofore unexamined aspect of post-transcriptional regulation in carcinogenesis. Our results will provide both new diagnostic/prognostic markers to identify patients with incurable metastatic disease and new druggable targets to create precision, individualized therapies.

Tier 1: Basic Science

PI: Paul Dayton, PhD, professor, Biomedical Engineering, Pharmacy DPMP
Co-Investigators: Yuliya Pylayeva-Gupta, PhD, assistant professor, Department of Genetics; Autumn McRee, MD, associate professor, Medical Oncology

Project Title: A Pilot Study in Ultrasound-Enhanced Pancreatic Cancer Immunotherapy

Abstract
The immunosuppressive tumor microenvironment creates a formidable challenge to treatment of pancreatic ductal adenocarcinoma (PDAC). Its resistance to the "gold standard" chemo- and radiation therapy and to immune checkpoint blockade, which has recently been FDA approved for other cancer types, is motivation for to develop new therapies for treating PDAC. Poor responses to therapy are thought to be due to profound immunosuppression, coupled with insufficient antigen presentation capacity as well as desmoplasia-driven compression of tumor vasculature. Recently, non-invasive focused ultrasound (FUS) has emerged as an exciting and highly novel immunomodulatory cancer therapy, with *several studies showing primary and metastatic tumor burden reduction and increased markers of*

immune system activation after ultrasound treatment. However, lack of knowledge regarding mechanisms of action with this very new technology as well as optimal ultrasound parameters to achieve consistently effective immunotherapy improvement presents a barrier to clinical or even widespread preclinical use. Here, we propose a rigorous pilot study of immunological biomarker changes in response to varying focused ultrasound parameters to both elucidate optimal ultrasound parameters as well as mechanism. Our proposed research will use a clinically meaningful orthotopic murine model of pancreatic cancer as well as rigorous assays for immunological markers. Ultrasound delivery will be varied across relevant therapeutic ultrasound parameter ranges (ablative, mild hyperthermia, low-intensity radiation force, and cavitation regimes, with and without microbubbles). This effort will inform our team and scientists in the field with a solid starting point for the development of ultrasound-enhanced immunotherapy strategies against PDAC, to be expanded with future applications for extramural funding.

Tier 1: Population Science

PI: Megan C Roberts, PhD, assistant professor, UNC Eshelman School of Pharmacy, Division of Pharmaceutical Outcomes and Policy, and director of Implementation Science in Precision Health and Society
Other Investigators: Christopher Baggett, PhD, assistant professor; Alan Kinlaw, PhD, MSPH, assistant professor; Katie Reeder-Hayes, MD, MBA, MSc, assistant professor; Ben Urick, PharmD, PhD, assistant professor; and Stephanie B Wheeler, PhD, MPH, professor.

Project Title: Linking medical record and claims data to better understand cancer outcomes within the UNC health care system

Abstract
Current data limitations challenge researchers' ability to measure the impact of precision medicine approaches on the quality of cancer care across the UNC Healthcare system. As these approaches become more widely implemented into cancer treatment and prevention, we must identify innovative datasets that include the right data to monitor precision medicine quality, access, costs, and health outcomes. To address this need, we propose the following specific aims: Aim 1. Assess the relative feasibility of multiple approaches for linking structured and unstructured clinical data in electronic health records from the Carolina Data Warehouse for Health (CDW-H) to the Cancer Information & Population Health Resource (CIPHR) dataset for 2015-2016; and Aim 2. Describe chemotherapy utilization among women who received Oncotype DX testing across the UNC Healthcare system in 2015-2016. This will be the first study utilizing linked CIPHR-CDW-H data, as well as the first to link CIPHR-CDW-H and unstructured EHR data. The expected outcomes from this study will be to demonstrate the feasibility of abstracting structured and unstructured data from the electronic health record, cleaning and discretizing those data as needed, and linking them to the CIPHR dataset. Using Oncotype DX as a test case will allow us to assess the impact of Oncotype DX testing on treatment choice, and in the future to measure long-term health outcomes prospectively. Once completed, this project will provide a powerful resource to examine precision medicine and cancer outcomes in the state of North Carolina and ultimately improve quality of care in the UNC Healthcare System.

Tier 1: Basic/Translational

PI: Tracy L Rose, MD, MPH, assistant professor, Division of Hematology/Oncology

Project Title: The Tumor Neoantigen Response to Chemotherapy and Chemo-Immunotherapy in Muscle-Invasive Bladder Cancer

Abstract
Neoadjuvant chemotherapy (NAC) is the standard of care for muscle-invasive bladder cancer (MIBC). Several immune checkpoint inhibitors are approved in the treatment of metastatic bladder cancer and combination chemo-immunotherapy trials are underway. In order to understand how the addition of immune checkpoint inhibitors to NAC modulates the anti-tumor immune response, we must first understand anti-tumor immune changes when NAC is given alone. The Kim lab has previously identified two molecular subtypes of MIBC, termed "luminal" and "basal." We have evidence that a subset of luminal tumors, which at baseline have a paucity of inflammation and immune checkpoint expression, become more heavily immune infiltrated after NAC. Further, the burden of tumor-specific proteins, termed neoantigens, is prognostic in bladder cancer and may independently predict response to immune checkpoint inhibition. We hypothesize that NAC elicits an anti-tumor immune response in the luminal subset of tumors leading to a decrease in predicted neoantigen burden that is not seen in basal tumors. We also hypothesize that the addition of immunotherapy to NAC will potentiate the anti-tumor immune response in luminal tumors with a further decrease in predicted neoantigen burden. To answer these questions, we will study the dynamic response of predicted neoantigens in subtypes of MIBC after NAC alone and NAC in combination with immune checkpoint inhibition via our ongoing biospecimen protocol and our phase II trial of neoadjuvant pembrolizumab and NAC in MIBC. These studies will assist the development and optimization of chemo-immunotherapy combinations in MIBC to improve treatment in this deadly disease.

Tier 1: Clinical/Translational

PI: Colette Shen, MD, PhD, assistant professor, Department of Radiation Oncology

Project Title: A pilot study investigating novel quantitative magnetic resonance imaging techniques to distinguish radiation necrosis versus tumor recurrence in brain metastasis following radiosurgery

Abstract
Stereotactic radiosurgery (SRS) is a standard treatment for patients with brain metastases, providing focused, high-dose radiotherapy while limiting cognitive side effects. However, an increasing problem is distinguishing radiation necrosis versus tumor recurrence following SRS, which can present with similar clinical and imaging characteristics. Accurate distinction between these two processes is critical for patient management and the decision between observation/supportive care or additional aggressive treatment. The gold standard is surgical resection for pathologic confirmation, which is invasive, difficult in poor surgical candidates, and potentially avoidable in cases of necrosis. Currently, magnetic resonance imaging (MRI) evaluation of intracranial tumors is based on qualitative T1- and T2-weighted data, with arbitrary units not amenable to quantitative analysis, leading to evaluation bias, inter-scan inconsistency, and diagnostic limitations. Here, we propose to utilize a novel magnetic resonance fingerprinting (MRF) approach to provide quantitative T1 and T2 data, with the goal of improving diagnostic accuracy of radiation necrosis versus active tumor. In Aim 1, we will evaluate MRF in two

small cohorts of patients whose status should be almost certain: patients with newly diagnosed brain metastasis (known tumor) and patients who have recently completed SRS for brain metastases (likely treatment effect/necrosis). In Aim 2, we will evaluate MRF in patients with question of radiation necrosis versus tumor recurrence in SRS-treated brain metastases, planned for surgery. The results of this pilot study would lead to a larger clinical study evaluating MRF as a potentially valuable diagnostic tool following radiation therapy in the brain.

Tier 1: Population Science

PI: Lixin Song, PhD, RN, associate professor, School of Nursing

Project Title: Feasibility Testing of Patient Reported Outcomes-informed Caregiving Education and Symptom management System (PROCESS): A Personalized mHealth Program for Cancer Symptom and Complication Management.

Abstract
Colon and bladder cancer (CBC) patients with newly created ostomies have unmet supportive care needs for managing multiple complex, interrelated symptoms and complications during post-treatment care transition from hospital to self-care at home. In-person programs have limited reach to the cancer population and have shown mixed effectiveness. mHealth programs have the potential to help a broader population mitigate the negative impact of the health conditions. However, lack of personalization and caregiver involvement reduces their relevance and usefulness. In this proof-of-concept study, our strong multidisciplinary team will conduct a pilot randomized clinical trial to test the feasibility of an innovative patient-caregiver-centered, personalized mHealth program, ***P****atient* ***R****eported-****O****utcomes-based* ***C****aregiving* ***E****ducation and* ***S****ymptom* ***S****ystem* (PROCESS), to enhance post-treatment supportive care for cancer patients and caregivers. PROCESS uses mHealth technology to provide both patients and caregivers continued access to self-care and management resources. PROCESS integrates PRO and objective data from wearable devices to continuously monitor patients' symptoms and complications after hospital discharge. The monitoring data will enable PROCESS to triage patient care based on the severity of their symptoms and complications, and provide self-care guidance with personalized content and delivery schedule for the symptoms and complication signs that patients have. PROCESS delivers personalized messages, tips and suggestions that are addressed to the patient or caregiver using his/her first name. Lessons learned from PROCESS will help to develop a new model to provide ongoing personalized self-care at home, complementary to professional care at the hospital, to help patients and caregivers manage complex health conditions following treatment.

Tier 1: Clinical/Translational

PI: Shivani Sud, MD, resident physician, Department of Radiation Oncology
Faculty Sponsor: Gaorav P Gupta, MD, PhD, assistant professor

Project Title: Application of circulating HPV DNA testing to management of cervical intraepithelial neoplasia

Abstract
Screening has significantly reduced the incidence of and mortality from cervical cancer through early

identification and treatment of cervical intraepithelial neoplasia (CIN) 2--3 with excisional or ablative surgical procedures;; however, these procedures increase the risk of poor obstetric and quality of life outcomes. Triage must balance preventing progression to invasive disease and avoiding overtreatment of lesions likely to regress and is resultantly complex, resource--intensive and requires multiple visits. Novel biomarkers indicative of disease burden are needed to more accurately risk--stratify and guide personalized treatment. Circulating HPV DNA (cHPVDNA) is a potential non--invasive biomarker to guide CIN management. cHPVDNA is detectable in plasma of patients with cervical cancer and CIN, albeit unreliably due to limited sensitivity of assays utilized in prior studies. We propose a novel application of our digital PCR assay validated as sensitive (89%) and specific (98%) for cHPVDNA detection in oropharyngeal cancer patients to management of CIN. Using paired urine and plasma samples, we will characterize the relationship between plasma, urine cHPVDNA levels and 1) CIN1 versus CIN2--3 pathology 2) CIN2--3 pre--excision and 2--4 weeks post--excision. In collaboration with UNC Gynecology, we will enroll three cohorts of 25, 30, 30 patients corresponding to 1) Control 2) CIN1 3) CIN2--3. Analysis of the control cohort will establish background signal in the assay. We will compare the proportion of detectable cHPVDNA levels between CIN1 and CIN2--3 cohorts using Fisher's exact test with 80% power, significance level of 10%. Paired t--test will be used to compare pre-- and post--excision cHPVDNA levels.

Tier 1: Population Science

Testing Oncology Care Quality Measures: Practice-level Variation and Measure Reliability

PI: Ben Urick, PharmD, PhD, assistant professor, UNC Eshelman School of Pharmacy

Co-Investigators: Hanna Sanoff, MD, MPH, associate professor; Jennifer Elston Lafata, PhD, associate professor; Justin Trogdon, MA, PhD, associate professor; Christopher Baggett, PhD, assistant professor

Abstract
The Oncology Care Model (OCM) has brought alternative payment models into oncology practice. Relying on quality measures to inform performance-based payments, oncology practices which generate savings and demonstrate sufficient quality can receive bonus payments. The impact of the OCM and OCM-type models on North Carolina oncology practices is unknown, and there is little evidence that the claims-based measures used to support the OCM can reliability separate provider impact from other influences on care quality. Therefore, to address these gaps, this research has the following three aims: 1) Measure variation in quality measure scores across all NC oncology practices; 2) Explore predictors of practice-level quality scores; and 3) Evaluate the ability of quality measures to detect provider impact. Treatment episodes will be identified following the OCM specifications and using 2016 administrative claims data from Blue Cross/Blue Shield of North Carolina and Medicare. Three quality measures used in the OCM will be constructed: 1) Hospitalization during treatment episode; 2) Emergency department visit during episode; and 3) Use of hospice for at least 3 days among those who have died during the episode. Quality scores will be aggregated at the provider level, and predictors of provider-level performance will be evaluated using linear regression models. Additionally, reliability for each measure will be evaluated using residual intraclass correlation coefficients as well as reliability scores. These results can inform the development of future oncology-focused APMs, as well as create a laboratory to further the development of oncology care models which best detect provider-level care quality.

Tier 1: Clinical/Translational

PI: Timothy Voorhees, MD, clinical fellow
Co-Investigators: Anne Beaven, MD, associate professor; Natalie Grover, MD, assistant professor; Jonathan Serody, MD, Elizabeth Thomas Professor of Medicine

Project Title: A Prospective Pilot Study Assessing the Immunomodulatory Effect and Clinical Activity of Programmed Cell Death Protein 1 Inhibition Following CD30 Directed Chimeric Antigen Receptor T-cell Therapy in Relapsed/Refractory Classical Hodgkin Lymphoma

Abstract
BACKGROUND: Hodgkin lymphoma (HL) is a B-cell malignancy, representing approximately 11% of all lymphomas seen in the United States, characterized by CD30+ multinucleated Reed- Sternberg cells within an extensive, ineffective immune infiltrate. Programmed cell death protein 1 (PD-1) antibody therapies have been studied in relapsed/refractory (r/r) HL with encouraging clinical activity; however, most patients eventually develop clinical progression. Our institution has experience with administering autologous CD30 directed chimeric antigen receptor T-cells (CAR-T) to patients with r/r HL. Despite high response rates with CAR-T therapy, clinical progression has been observed. Preliminary data from patients who progressed on CD30 CAR- T cell therapy and subsequently were re-challenged with anti-PD-1 therapy has shown surprising clinical response. In this prospective pilot study, we aim to determine the immunomodulatory effect of CD30 CAR-T cell therapy and the subsequent ability to rescue peripheral T-cell exhaustion with anti-PD-1 therapy. OBJECTIVES: 1) To estimate the objective response rate (ORR) and progression free survival (PFS) of anti-PD-1 therapy after progression on CD30 CAR-T cell therapy. 2) To determine the immunomodulatory effect of CD30 CAR-T cell therapy and the ability to rescue peripheral T-cell exhaustion by anti-PD-1 therapy in r/r classical HL. RESEARCH APPROACH: In this prospective pilot study, we will enroll 10 patients with r/r classical HL who have previously progressed on anti-PD-1 therapy, have received CD30 CAR-T cell therapy and have evidence of progression. Patients will be offered re-challenge of anti-PD-1 therapy (physician choice: FDA approved nivolumab or pembrolizumab) per standard of care in r/r classical HL. Peripheral blood (PB) samples will be collected from patients at the time of progression after CD30 CAR-T cell therapy as well as at 3 and 6 weeks after initiating anti-PD-1 therapy. We will also have access to peripheral blood samples prior to CD30 CAR-T cell therapy, acquired during a previous study. PB samples will be immunophenotyped by mass cytometry and will undergo T-cell receptor (TCR) sequencing to establish evidence of clonal expansion. Clinical response will be determined at 12 weeks after initiating anti-PD-1 therapy as measured by the Lymphoma Response to Immunomodulatory Therapy Criteria. SIGNIFICANCE: This pilot study will be the first to analyze the ability of CD30 CAR-T cells to result in immunomodulation. It will also be the first to prospectively assess the clinical response of re-challenging classical HL patients with anti-PD-1 therapy. Positive results with evidence of immunomodulation or clinical response would provide rationale for combining CD30 CAR-T cell therapy and anti-PD-1 therapy sequentially in a future prospective trial.

Tier 1: Clinical/Translational

PI: Andrew Z. Wang, MD, associate professor, Radiation Oncology
Co-investigator: Jenny P. Ting, PhD, William R. Kenan, Jr. Professor

Project Title: The effects of short chain fatty acid supplementation on the quality of life and treatment-related toxicities in patients receiving definitive abdominopelvic radiotherapy: A randomized phase II study

Abstract
Radiation therapy is a critical treatment modality in the management of urologic, gynecologic and gastrointestinal malignancies. Although advances in treatment delivery techniques have led to reductions in cancer and treatment-associated morbidity and mortality, normal tissue toxicity remains a limitation to dose escalation and treatment tolerance. Among patients receiving abdominopelvic radiation therapy alone or as multimodality treatment in combination with surgery or chemotherapy, over 50% develop clinically meaningful toxicity. Pharmacologic strategies to reduce normal tissue damage represent a tremendous unmet need in radiation therapy. Short chain fatty acids (SCFA) are fatty acids with fewer than 6 carbon atoms ingested or formed during bacterial fermentation of partially- and non-digestible polysaccharides carbohydrates. A combination of preclinical and clinical data support the hypothesis that oral supplementation with potent formulations of SCFA during radiation therapy will reduce acute gastrointestinal toxicity such as severe diarrhea, cramping, pain and potentially decrease the incidence of radiation-induced late bowel toxicity. Thus, we propose a phase II study of the efficacy of SCFA supplementation for reducing incidence and severity of patient reported acute gastrointestinal toxicity among those receiving abdominopelvic radiation. This trial will be preceded by a safety run-in. The phase II trial will have 80% power to detect a 23% difference in patient-reported Grade 2 or higher gastrointestinal toxicity (placebo proportion, π_1, of 0.50, SCFA proportion π_2, of 0.27) with 61 patients per arm using Fisher's exact test with 0.05 one-sided significance.

Tier 1: Basic Science

PI: Christopher Whitehurst PhD, assistant professor, Microbiology and Immunology

Project Title: Towards Discovery of a Chemical Probe Targeting the Virally Encoded Deubiquitinating Activity of Epstein-Barr Virus

Abstract
Epstein-Barr Virus (EBV), a human tumor virus, is the causative agent of mononucleosis and immunoblastic lymphomas. EBV is strongly associated with Burkitt's lymphoma, Hodgkin's lymphoma, and nasopharyngeal carcinoma (NPC). Additionally, recent studies suggest that EBV has a pathogenic role with the onset of Multiple Sclerosis (MS). Approximately 90% of the world's population is infected with EBV, but most do not present disease. However, for those that do develop EBV-related illness there remains no directed small molecule therapy. EBV-triggered disease, causing debilitating illness and death, remains a world-wide problem. Interestingly, EBV expresses a unique protein (BPLF1) that possesses deubiquitinating activity. BPFL1 is known to regulate both cellular and viral target activities, yet it remains largely unstudied. Our work has implicated BPLF1 in a wide range of viral and cellular processes including infectivity (90% reduction with knockout of BPLF1), viral DNA replication, and DNA repair. Also we recently reported surprising new findings that knockout of BPLF1 delays and reduces human B-cell immortalization and lymphoma formation in humanized mice. The aim of this proposal is to discover and characterize the first-in-world small molecule inhibitors of BPLF1 deubiquitinating activity. The goals of this proposal are to 1) use high throughput screening to identify novel chemotypes for a lead optimization effort and 2) produce further validation that small molecule inhibition of BPLF1 deubiquitinating activity is a promising avenue for treating diseases caused by EBV infection. This work will lay the foundation for a chemical probe and drug discovery effort to combat EBV-associated disease.

Tier 2: Population Science

PI: Ashley Leak Bryant PhD, RN, assistant professor, School of Nursing

Project Title: Feasibility of a Novel Symptom and Supportive Care Intervention for Adults with Acute Myeloid Leukemia

Abstract
Adults with acute myeloid leukemia (AML) require intensive chemotherapy and prolonged hospitalization of 4-6 weeks, placing them at risk for debilitating symptoms and declines in function. A comprehensive intervention is needed because symptoms interfere with activities of daily living (ADLs) leading to functional decline. We propose a symptom management and supportive care intervention in which the patient works with the integrated team (RN, PT, OT) to understand their symptoms and the barriers that symptoms create resulting in lack of engagement in ADLs. The patient and integrated team develop a tailored symptom management and ADL plan and revise as needed. The RN will assess, monitor, and manage symptoms; the OT and PT will assess function and focus on maintaining function necessary for daily tasks. All intervention patients will be seen daily by the RN for symptom monitoring and management. The PT and OT will assess patient's function twice weekly. In aim 1, we assess feasibility of the intervention in twenty adults with AML. Feasibility will be measured by recruitment rate, retention rate, attrition, number of adverse events, and completion rate of self- reported data. To assess acceptability (aim 2), we will conduct semi-structured interviews near discharge and 2 weeks post-discharge. If this patient and multidisciplinary team collaborative intervention has favorable outcomes in adults with AML during intensive chemotherapy, we will have preliminary evidence to support a larger efficacy trial (multi-site). This work is significant because it may be transferable to other populations with prolonged hospitalizations and who are at-risk for functional decline.

Tier 2: Clinical/ Translational

PI: Catherine C. Coombs, MD, assistant professor
Co-Investigator: Matthew I. Milowsky, MD, George Gabriel Villere Distinguished Professor of Bladder and Genitourinary Cancer

Project Title: Examining the interaction between clonal hematopoiesis and clinical outcomes among patients with metastatic castration-resistant prostate cancer treated on A031201

Abstract
Clonal hematopoiesis (CH) denotes the presence of somatic mutations in hematopoietic cells[1,2]. Individuals with CH are at increased risk for hematologic neoplasms, estimated at 0.5-1.0% annually and have shortened overall survival (OS), partially attributed to increased cardiovascular mortality. The term "CHIP" (clonal hematopoiesis of indeterminate potential) describes individuals with CH who have mutations with variant allele frequencies (VAF) of ≥2% in absence of blood count abnormalities. In a large study of advanced solid tumor patients, CH was associated with shorter OS among patients carrying driver mutations at VAF ≥10%. Death from transformation to hematologic malignancies did not explain the detriment to survival, as the overwhelming majority of patients died from progression of the non-hematologic tumor. Subsequently, it has been hypothesized that the inferior OS may be due to CH promoting tumor progression through cell non-autonomous effects, though this requires further study. Examining the interaction between CH and cancer progression is challenging, as cohort-based

populations include patients with diverse cancers who received different prior therapies including radiation and chemotherapy, which influence the presence of CH in addition to different levels of intrinsically refractory disease. CH has been demonstrated in prostate cancer patients in broad and dedicated studies, and indirect evidence supports that CH could be associated with a decrease in responsiveness to hormone-directed therapy. We propose to study the interaction between CH and responsiveness to cancer-directed therapy in the chemotherapy-naïve population of patients with castration-resistant prostate cancer that were treated with anti-androgen therapies including enzalutamide and abiraterone acetate under protocol A031201.

Tier 2: Basic/Translational

PI: William Y. Kim, MD, professor, Division of Hematology/Oncology, Department of Medicine Department of Genetics
Co-Investigators: Gianpietro Dotti, MD, professor, Microbiology and Immunology; Sara Wobker, MD, assistant professor, Pathology and Laboratory Medicine

Project Title: Development of chimeric antigen receptor (CAR) T-cell therapy for bladder cancer

Abstract
Bladder cancer is the fifth most common malignancy, with an estimated 76,960 new cases and 16,390 deaths in the United States in 2016. Thirty percent of bladder cancer patients have muscle invasive bladder cancer (MIBC) and unfortunately approximately 50% of MIBC patients relapse with metastatic disease. Although patients with metastatic bladder cancer are treated with cisplatin-based chemotherapy, their median survival remains limited to 10-12 months. Recently, the FDA has approved multiple immune checkpoint (IC) inhibitors that block the PD-1/PD-L1 axis documenting the immunotherapy responsiveness of bladder cancer. Nonetheless, the therapeutic efficacy of IC therapy is limited. While CAR-T cell therapy has had remarkable efficacy in treating hematologic malignancies, this has not extended to solid tumors. One significant reason for the limited efficacy is that current solid tumor targets are broadly expressed in tissues throughout the body (i.e. HER2). UPK2 expression is highly restricted to the terminally differentiated umbrella cells of the urothelium and is highly expressed in a subset of luminal bladder cancers. Given bladder cancer's proven immune responsiveness to IC therapy and the highly restricted expression of UPK2 in normal cells, we hypothesize that UPK2, akin to CD-19 in acute lymphoblastic leukemia, will be a highly specific and effective target for a subset of bladder cancers of the luminal molecular subtype. If successful, this proposal will develop an UPK2 specific antibody and generate preclinical validation of UPK2 as a CAR T cell target, propelling our anti-UPK2 CAR T cells into clinical trials.

Tier 2: Population Science

PI: Jennifer Elston Lafata, PhD, professor, Eshelman School of Pharmacy

Project Title: Text Messaging to Enhance the Use of Patient-targeted Decision Support among Diverse Populations

Abstract
Despite clear evidence of morbidity and mortality benefits, colorectal cancer (CRC) disproportionately effects low income and racial/ethnic minority populations. These vulnerable

populations also disproportionately underutilize CRC screening. Targeting patients for support at the time of a CRC screening decision is important as almost half of patients with a physician recommendation do not get screened, and patients with unanswered questions or a test recommendation inconsistent with their preferences are less likely to be screened. How to provide decision support in practice-integrated ways remains a challenge. While online patient portals are appealing for reasons of practice-integration, their use runs the risk of exacerbating health disparities given well-documented differences in portal use. Text messages may be an effective way to engage diverse subgroups of the population, as cell phone ownership is now ubiquitous and texting is widely used. We propose to use user-centered design and co-production to adapt known effective CRC screening decision aid content for use with text messaging. We will examine responses to text messages via an online panel and conduct user testing and a pilot study to iteratively develop a text-messaging CRC screening decision support program that has high perceived usability and intentions to use, paying specific attention to these outcomes among subgroups of the population defined by income and race. Using prompted and free-response question features available within the programs, we will collect and categorize potential patient questions to inform database development for future automation with machine learning. Our specific aims include: (1) to develop text messages for use among diverse populations; (2) to use in-depth interviews and focus groups to illustrate the acceptability, feasibility, and practice-integration of the text-messaging program among diverse stakeholders; (3) to illustrate the potential effects of the text-messaging program on patient CRC screening intentions, knowledge, and self-efficacy; and (4) to determine expected patient questions and develop a bank of evidence-based responses. Results from the proposed feasibility study will inform the development of a text-messaging program for diverse populations. Results will also inform how practice-integrated programs may beneficially impact cancer screening-related outcomes and build critical infrastructure for future automated decision support—factors critical to scalability and widespread adoption. Project results will be used as preliminary data for a pragmatic clinical trial submitted to NCI and NIMHD under PAR-19-093.

Tier 2: Basic Science

PI: Lishan Su, PhD professor of Microbiology and Immunology
Co-Investigators: Gianpietro Dotti, MD, professor of Microbiology & Immunology

Project Title: Tumor-Associated pDC in Ovarian Cancer Tumor MicroEnvironment/TME and Immunotherapy

Abstract
The majority of women with advanced ovarian cancers (OC) have shown poor responses to current immunotherapies. Understanding the OC tumor microenvironment (TME) is critical to the development of potent immunotherapy approaches including adoptive immunotherapy with chimeric antigen receptors T cells (CAR-T). We have recently identified the pDC/IFN-I axis that plays a critical role in suppressing host immunity in inflamed tissues caused by persistent HIV infection. Interestingly, persistently activated tumor associated pDC (TA-pDC) are also induced in certain human tumors including OC. More importantly, the presence of TA-pDC in these tumors is associated with poor prognosis and poor response to current therapies. The long-term goals will elucidate the immunologic mechanisms of tumor-associated/TA-pDC in the OC-TME that contribute to immune suppression, and to develop novel therapeutics (combining pDC depleting antibody

with B7-H3/CAR-T cells) in BDCA2 Tg/B6 mouse OC models and in the novel humanized mouse model with **H**uman **I**mmune and human OC **T**umor cells (OC-HIT mice). I hypothesize that TA-pDC in the OC-TME play a critical role in the immune suppressive TME and depletion of TA-pDC in OC-TME will also reverse immune suppression, rescue anti-OC T cells and enhance CAR-T cells in treating OC. We will investigate the mechanism of TA-pDC in programing the OC-TME and modeling novel CAR-T therapeutics in both immunocompetent syngeneic OC B6 mouse and in human OC-HIT mice. Importantly, we will assess whether TA-pDC depletion will show enhanced antitumor activity of CAR-T cells in these OC models.

Tier 3, Targeted RFA for Clinical Pilots

PI: Michael S. Lee, MD, assistant professor, Division of Hematology/Oncology, Department of Medicine
Co-Investigators: Federico Innocenti, PhD, associate professor; Temitope Keku, PhD, professor; Joel Parker, PhD, associate professor

Project Title: Clinical and immunologic effects of immune checkpoint inhibitors and panitumumab in colorectal cancer and tumor-immune-microbiome interactions

Abstract
Immune checkpoint inhibitors have proven to be ineffective in the 97% of metastatic colorectal cancers (CRC) that are microsatellite stable (MSS), and MSS CRC is generally considered an immunologically cold tumor. However, there is significant interpatient heterogeneity, with distinct gene expression-defined subtypes with varying tumor-intrinsic and stromal biologic signatures, including varying immune cell composition. The CRC tumor microenvironment is further influenced by gut microbes, such as Fusobacterium, which is aberrantly found in up to 43% of CRCs. The association between these intrinsic and microenvironmental factors with immune cell infiltration is unclear, and further study to better understand how to provoke an anti-tumor immune response and identify prognostic and potentially predictive biomarkers for novel immunotherapeutic approaches is needed. Indeed, novel immunomodulatory combination approaches are needed in the clinic. Anti-EGFR antibodies like panitumumab are currently standard for patients with KRAS, NRAS, and BRAF wild- type CRC, but while they inhibit EGFR-mediated mitogenic signaling, they also induce immunogenic cell death through CD8+ T-cell activation. However, the efficacy of anti-EGFR therapies is limited in duration, and ultimately upregulation of immunosuppressive regulatory T cells and macrophages expressing CTLA-4 and PD-L1 occurs, appearing to contribute to therapeutic resistance. Thus, we developed a multicenter, single-arm, investigator-initiated clinical trial of ipilimumab, nivolumab, and panitumumab in KRAS, NRAS, and BRAF wild-type MSS metastatic CRC. We aim to determine clinical activity of this combination and pharmacodynamic effects on peripheral immune cell activation. We additionally will study associations of immune cell signatures within CRCs with gene expression subtypes and gut microbial composition.