Tier 1: Population Sciences

PI: Emma Allott, PhD, Research Assistant Professor, UNC Gillings School of Global Public Health

Project Title: Molecular profiling of prostate cancer to understand mechanisms contributing to racial disparities.

Abstract
African Americans (AAs) have the highest prostate cancer incidence in the US and a prostate cancer-specific mortality rate more than double that of whites. Non-biologic factors, including socioeconomic status and access to care, play a role but do not completely explain the prostate cancer disparity and although biologic mechanisms contribute, they are not well understood. A transdisciplinary approach that integrates epidemiologic, clinical and tumor biomarker data is required, given that the mechanisms contributing to prostate cancer racial disparities span each of these research disciplines. The objective of the work outlined in this proposal is to build a molecular epidemiology prostate cancer cohort to discover biologic mechanisms contributing to prostate cancer racial disparities, using the infrastructure of the Health Registry/Cancer Survivorship Cohort (HR/CSC) and the expertise in tumor profiling methods at UNC. We have identified 147 prostate cancer cases who underwent radical prostatectomy (RP) at UNC and who participated in the HR/CSC at a recruitment rate of approximately 30 RP cases per year. Using RNA counting methods (Nanostring) to measure an established androgen receptor (AR) activity gene expression signature in tumor and adjacent normal tissue specimens from these participants, we will examine differences in AR activity between AA and white participants. This work will establish the feasibility of building a molecular epidemiology prostate cancer cohort at UNC, and identify AR activity as a potential biologic pathway that could targeted alongside other treatments and interventions to help reduce racial disparities, and to improve prostate cancer-specific outcomes for all men.

Tier 1: Clinical/Translational

PI: Laura Bowers, PhD, MPH, Postdoctoral Fellow, UNC Gillings School of Global Public Health, and Stephen Hursting, PhD, Professor, UNC Gillings School of Global Public Health,

Project Title: Obesity-associated chemotherapy resistance in triple-negative breast cancer: The Role of leptin-induced tumor-initiating cell enrichment

Abstract
Obesity is a significant global public health problem associated with greater risk and progression of numerous diseases, including breast cancer. Excess adiposity has been correlated with increased recurrence and lower survival rates in all breast cancer subtypes, including triple- negative breast cancer (TNBC). In addition, obese patients do not respond as well as normal weight women to cytotoxic chemotherapy. Given that the highly aggressive TNBC subtype is still primarily treated with these drugs due to the tumors' lack of specific molecular targets, chemoresistance is likely a major contributor to the poorer outcomes

observed in obese TNBC patients. Consequently, greater understanding of the mechanism(s) mediating this resistance is imperative to improving prognoses in this population. Enhanced tumor-initiating cell (TIC) enrichment may be a key factor in the link between obesity and chemoresistance in TNBC, as we have demonstrated that obesity promotes TIC characteristics in pre-clinical models of TNBC, and TICs are thought to be capable of evading the cytotoxic effects of chemotherapy. Research from our collaborators and others also suggests that leptin signaling is the primary mediator of obesity- induced TIC enrichment, and elevated serum leptin levels and breast tumor leptin receptor expression have been independently linked to a worse breast cancer prognosis. Therefore, we propose to test if obesity-associated leptin signaling contributes to chemotherapy resistance in TNBC via TIC enrichment and whether a reduction in leptin signaling improves chemotherapy response in a pre-clinical model of obesity and TNBC.

Tier 1: Translational

PI: Timothy Gershon, MD, PhD, Associate Professor, Department of Neurology

Project Title: Developing KIF11 inhibition as a novel medulloblastoma therapy in mice

Abstract
New approaches are needed for medulloblastoma, the most common malignant brain tumor in children. Current therapy, with craniospinal radiation and chemotherapy while often effective, produces unacceptable long-term brain injury. Medulloblastoma is highly mitotic and markedly sensitive to DNA damage, suggesting the anti-mitotic agents may be particularly effective therapies that could specifically target tumor cells. Established antimitotic agents, however, are particularly neurotoxic because they target microtubules. As a result, all clinically tolerable conventional anti-mitotics have poor blood-brain barrier penetration. We propose to test an alternative approach to targeting mitosis, using kinesin inhibition. Unlike microtubules, kinesins are process specific, and the mitotic kinesin KIF11 can be targeted without disrupting brain function. We have developed a formulation of a small molecule KIF11 inhibitor SB743921 solubilized in polyethylene glycol (PEG- SB), that crosses the blood brain barrier when injected IP in mice. Our preliminary data show that a single dose of PEG-SB causes mitotic arrest, DNA damage and apoptosis in medulloblastomas in vivo. We now propose to develop a regimen of this novel formulation that is tolerated in mice and to test this regimen in transgenic mice that develop spontaneous medulloblastoma. The goal of these pilot studies is to determine whether PEG-SB exerts a clinically relevant antitumor effect as a single agent. If so, we will plan future studies on how KIF11 inhibition may be integrated into conventional therapy, potentially allowing for reduced radiation and improved outcomes for patients with medulloblastoma.

Tier 1: Basic/Translational Science

PI: Zhanhong Wu, PhD, an Assistant Professor, Department of Radiology

Co-Investigator: Jen Jen Yeh, MD, Associate Professor, Departments of Surgery and Pharmacology

Project title: Detection of pancreatic cancer metastasis using PET agent targeting neurotensin receptor

Abstract
Pancreatic cancer is one of the deadliest human malignancies, with an extremely poor 5-year survival rate below 6%. Although there has been some improvement in the strategies used to diagnose and treat pancreatic cancer, its prognosis is still poor, due to a lack of efficient methods to detect pancreatic carcinoma, the difficulty of clearly differentiating pancreatic cancer from benign pancreatic lesions, and its aggressive progression. There is clearly a need to develop new diagnostic and therapeutic methods targeting both primary and metastatic pancreatic cancer. Accumulating evidence suggests that neurotensin receptors (NTRs) play key roles in pancreatic adenocarcinoma growth and survival. Both our preliminary research and literature suggest that well differentiated human pancreatic carcinomas bear high density of NTR-1 expression as compared with its expression in normal human pancreas and in chronic pancreatitis, as well as in endocrine pancreatic tumors. Clearly, NTR-1 could potentially become important components of pancreatic cancer diagnosis and treatment. In this application, we aim to evaluate our lead NTR-1 targeted agent in detecting small pancreatic cancer metastasis. The success of this novel imaging approach could not only lead to novel imaging approach for the detection of pancreatic cancer metastasis, but also help us better predict which patients and individual tumors are likely to respond to novel interventions targeting NTR-1 (patient screening) in the future.

Tier-1: Clinical/Translational

PI: David Lalush, PhD, Associate Professor, UNC and N.C. State Joint Department of Biomedical Engineering

Co-investigators: Kandace McGuire, Department of Surgery; Shumin Wang, Joint Department of Biomedical Engineering, UNC and NC State; Cherie Kuzmiak, Department of Radiology; and Terence Wong, Department of Radiology

Project Title: Utility of PET/MR in Surgical Planning for Breast Cancer Treated with Neoadjuvant Chemotherapy

Abstract
Neoadjuvant chemotherapy in patients with operable breast cancer has been shown to increase the proportion of candidates for breast-conserving surgery versus mastectomy with no increase in local recurrence rate, and also to improve the correlation of pathological complete response with long-term outcomes. It is critical to utilize all available information when planning surgery in order to optimize efficacy and reduce the likelihood of local recurrence and the need for repeated surgical intervention. Both PET and MRI have been used separately in the assessment of response to neoadjuvant therapy; a logical next step is to evaluate the utility of simultaneous PET and MRI for assessment of treatment response, the impact on surgical

planning, and the correlation with pathologic outcomes. This project will examine the ability of qualitative and quantitative measures derived from simultaneous 18F-FDG-PET and MRI (including anatomic imaging and dynamic contrast enhancement) to contribute to surgical planning decisions. The project will enroll N = 25 subjects with operable breast cancer who will receive neoadjuvant chemotherapy followed by surgery. PET-MRI scans will be taken at pre-treatment and post-treatment time points, and evaluated for changes in standardized uptake values (SUV) from PET as well as tumor size and perfusion functional measures from MRI. Post-surgery histology will be used to classify patients based on response to therapy. The first aim will involve the development of an eight-channel breast coil for the PET-MRI scanner to enable clinical-equivalent breast MRI. The second aim will examine the correlations between pre-treatment and post-treatment imaging metrics and response groupings of subjects based on surgery type, response to therapy, and residual tumor burden. The third exploratory aim will develop an optimal quantitative metric combined from PET and MRI results and assess its ability to classify patients based on (a) surgical management and (b) pathological outcomes.

Tier 2: Population Sciences

Melissa Troester, PhD, Associate Professor, UNC Gillings School of Global Public Health

Co-PI: Cherie Kuzmiak, DO, Associate Professor, Radiology

Project Title: Toward Risk Stratification of Screening False Positives: Biological Discovery in TMIST

Abstract
Mammography reduces breast cancer mortality, but also produces false positives resulting in negative psychological consequences, direct financial costs, and other complications. Discovery of biomarkers for risk stratification of false positives has been impeded by several challenges. First, there are few benign biopsy cohorts with sufficient size and follow up for invasive outcomes. Second, benign biopsies are small, paraffin- embedded specimens and therefore immunohistochemistry has been the primary means of molecular study. Our team has optimized RNA expression analyses and digital histologic analysis of benign breast. Simultaneously, UNC is a national leader in breast tumor profiling, and we have optimized Nanostring for large epidemiologic studies of paraffin specimens. The current proposal leverages these strengths in context of the Tomosynthesis Imaging Screening Trial (TMIST). The TMIST international clinical trial randomizes women to digital mammography (DM) or the next generation tomosynthesis (TM) for screening and will collect false positives specimens and follow the patients over time. The current proposal seeks to conduct molecular profiling (Aim 1) of false positives (n=1000) with three signatures: the PAM50 tumor-like vs. normal-like, proliferation high vs. low, and p53 mutant-like vs. wildtype. The study will also perform digital histology analysis (Aim 2) using published algorithms, and will compare molecular and histologic data (Aim 3). Characteristics of false positives will be compared between DM and TM arms, and according to patient characteristics (i.e. age and mammographic density), leading to future external proposals assessing these markers as predictors of invasive breast cancer risk.

Tier 2: Basic

PI: Jonathan Serody, MD, Professor of Medicine, Microbiology and Immunology

Project Title: Imaging PD-1 T/CAR-T cell Tumor Interaction and Vaccine Function in vivo

Abstract
There has been a revolution in the treatment of patients with cancer using immunotherapy. Despite the promise of immune-based approaches, with the exception of metastatic melanoma, the response rate is less than 30% for patients treated with checkpoint inhibition. Similarly, there is substantial interest in the use of adoptive cell therapy in the treatment of malignant disease. However, the response rates for the treatment of epithelial malignancies with CAR-T cells is modest with less than 10% of patients responding to HER-2/neu- CAR-T cell treatment. Despite the significant clinical activity of checkpoint inhibitors, their mechanism of activity at the site of tumor growth is not clear. PD-1 can bind two ligands in the tumor microenvironment, PDL-1, which is broadly expressed and PDL-2, which is solely expressed by antigen presenting cells (APC). The function of these interactions in the tumor microenvironment is not clear. To address these questions, we generated two novel mouse models. The first has TdTomato under control of the endogenous PD-1 locus. Thus, any cell in the tumor microenvironment that expresses PD-1 expresses TdTomato. The second is a PD-1 fate reporter model that expresses YFP in any cell that has expressed PD-1. Finally, we have developed a novel Neu-based system using a mouse anti-Neu ScFv and Neu transgenic mice that allows us for the first time to evaluate how anti-PD-1 therapy effects on target off/on tissue events mediated by CAR-T cells. These tools allow us to ask novel questions to address the role of PD-1 in the tumor microenvironment.

Tier 2: Basic Science

PIs: G. Greg Wang, PhD, Assistant Professor, Department of Biochemistry and Biophysics, and Stephen Frye, PhD, Professor, UNC Eshelman School of Pharmacy

Project Title: Decipher the role of DNA methyltransferase 3A (DNMT3A) mutation in acute myeloid leukemia

Abstract
Acute myeloid leukemia (AML) is a devastating cancer with a 5-year survival rate of only 26% and a need for development of new treatments. Recent sequencing studies of AML patient samples show that AML frequently acquires combinational gene mutation 'hitting' the *FLT3-RAS* kinase pathway as well as *DNMT3A*, a gene encoding a *de novo* DNA methyltransferase and epi-genomic regulator. *DNMT3A* mutations occur in >20-30% of AMLs making it one of the top three most frequently mutated genes in human AML. *DNMT3A* mutations also correlate with poor prognosis and AML relapse. However, *animal models for studying DNMT3A mutations are recurrently lacking and the role of this prevalent mutation in AML pathogenesis remains elusive*.

To model human disease, we have recently shown, *for the first time*, that somatic mutation of *DNMT3A* promotes malignant transformation and accelerates AML development in mice by using a *RAS* mutation as the cooperating oncogenic event. Genomic profiling studies of this novel AML model further demonstrated that *DNMT3A* mutation alters tumor cell epi-genome inducing abnormal up-regulation of stem cell-specific transcription factors and pro-survival factors. The goal of this Tie2 Stimulus proposal is (i) to further determine epigenetic mechanisms essential for *DNMT3A* mutation-induced AML and (ii) to elucidate gene pathways through which *DNMT3A* mutation promotes AML development. *Completion of the proposed research should fill in a knowledge gap regarding the role of DNMT3A mutation in deadly AMLs; as epigenetic pathways are considered as 'druggable', the proposal will also have immediate impact on development of new therapeutics for DNMT3A-mutated AML*.

Tier 2: Population Sciences

PIs: William Wood, MD, Associate Professor, and Ashley Freeman, MD, clinical fellow in the UNC School of Medicine

Project Title: Impact of geographic region, treatment facility, and Physician Network Characteristics on Outcomes for patients with acute leukemia and multiple myeloma in North Carolina

Abstract
Population-based studies have established the presence of survival disparities for hematologic malignancies according to sociodemographic variables, but the underlying cause for these disparities remains unclear. We recently demonstrated that survival for patients with acute myeloid leukemia in North Carolina varies according to geographic region. Specifically, residence in three of nine Area Health Education Center regions was associated with increased mortality (HR range 2.00 to 3.88, $p<0.01$) when controlling for other sociodemographic variables. Differences in local treatment facilities or referral patterns may be influencing outcomes. Missing from our previous study, and all prior population-based studies of adult hematologic malignancies, is information about the providers caring for these patients. Social network analysis (SNA) is an innovative technique that can be employed to understand how providers work together to care for complex patients. Our goal in this project is twofold. First, we will leverage the UNC Lineberger Integrated Cancer Information and Surveillance System (ICISS) to characterize survival disparities for acute leukemia (AL) and multiple myeloma (MM) in North Carolina by geographic region and type of treating facility. Second, we will apply SNA methods to identify physician networks and explore how features of those networks affect outcomes. This project will be the first in the nation to apply SNA to the study of disparities for any hematologic malignancy. Information from this study has the potential to establish SNA as an important methodology in disparities research and to improve outcomes for patients in North Carolina by informing statewide referral policies.

Tier 2: Clinical/Translational

PI: Shumin Wang, PhD, Assistant Professor, UNC & NC State Joint Department of Biomedical Engineering

Co-Investigators: David Lalush, Associate Professor, UNC/NCSU Joint Department of Biomedical Engineering; Bhishamjit S. Chera, Associate Professor, Department of Radiation Oncology; and Benjamin Y Huang, Associate Professor, Department of Radiology

Project Title: A novel 32-channel 3.0 Tesla PET/MRI Receiver Coil Array for Fast and High Resolution Head and Neck Cancer Imaging

Abstract
Despite the fact that PET/MRI is available to canner diagnosis, staging, and treatment planning, its translational values for clinical science and practice have been significantly limited by the inferior performance of the available radio-frequency coil for head/neck cancer imaging at the BRIC. Low signal-to-noise ratio in the head/neck region, low image acquisition speed, and the lack of head immobilization mechanism, to name a few, are severe concerns of radiologists and radiation oncologists. Moreover, there are no commercially available RF coils better designed to solve these issues. This application is a collaborative effort among a RF coil specialist, a PET/MRI imaging specialist, a radiation oncologist, and a radiologist for the Imaging and Oncology Targeted RFA. We propose to devise a novel high-end 32-channel PET/MRI receiver coil array for head/neck cancer imaging aiming to overcome limitations and difficulties associated with commercial coils. Specifically, the devised coil will dramatically improve SNR, which in turn allows enhanced spatial resolution, minimized subject motion, and the incorporation of MRI cancer imaging protocols. If successful, this instrument will be the first and the only dedicated 32-channel head/neck PET/MRI imaging coil in the world. This uniqueness will give UNC-Chapel Hill another huge advantage for cancer imaging and related research in its world-leading cancer research facilities.

Tier 3 Awards
PI: Ian Davis, MD, PhD, Associate Professor, UNC School of Medicine

Co-Investigators: Stephen Frye, PhD Fred Eshelman Distinguished Professor, Eshelman School of Pharmacy; Gary Johnson, PhD, Kenan Distinguished Professor and Chair, Department of Pharmacology; and Samantha Pattenden, PhD, Research Assistant Professor, Eshelman School of Pharmacy

Project Title: Chromatin Architecture as a platform for drug development

Abstract
Changes in chromatin organization associated with cancer can be the consequence of specific mutations in chromatin regulators or the product of aberrant differentiation or signaling pathways. Chromatin as a focus for therapeutic intervention remains in its infancy in part because of the limited validation of molecular targets. Novel discovery strategies offer the opportunity to break this logjam and infuse the development pipeline with potential

therapeutic leads. This proposal brings together three distinct scientific projects that explore this challenge at the interface of chromatin biology and human cancer. Each project will be supported by a robust, dynamic and synergistic interaction with two critical scientific cores. A Chemical Biology Core will design and synthesize chromatin focused, drug-like, small molecule libraries for hit discovery and carry out hit to probe optimization and tool synthesis in close collaboration with project biologists. A Chemical Biology Screening Core will optimize, implement, and interpret screening efforts building from a newly developed broadly applicable chromatin signature screening strategy. The interface between the Projects and the Cores is classified in phases. Phase I: identify and validate regions of disease-specific chromatin signature for screening; Phase II: development and application of the screen; Phase III: medicinal chemistry hit to probe optimization, target identification and validation. The central goal of this proposal is the discovery of novel chromatin-based mechanisms and potential therapeutics that disrupt cancer-specific pathways in tumors. Focusing on chromatin structure and regulation in both our screening strategies and small molecule libraries greatly enhances our ability to identify relevant compounds directly linked to critical epigenetic regulatory pathways. We are requesting funding to advance each project from their current phase as a multi-stage proof- of-concept enabling a forthcoming P01 proposal. Project 1 builds from an initial application of chromatin screening that assesses the effects of small molecules targeted toward chromatin regulatory proteins based on a specific, disease-associated chromatin signature (Phase III). This project, based on Ewing sarcoma, a highly malignant tumor of children and young adults, focuses on chemical probe target identification, advanced mechanistic, and preclinical studies. Project 2 applies this screen to target a transcription factor-dependent chromatin signature critical to luminal breast cancer (Phase II). We will validate this chromatin signature and perform the screen. Project 3 addresses the epigenetic changes associated with differential kinase inhibitor resistance in triple negative breast cancer (Phase I). We will identify a relevant chromatin signature which will be annotated with recognized chromatin features and use this signature to perform a comprehensive small molecule screen.

PI: D. Neil Hayes, MD, MPH, Associate Professor of Medicine

Project Title: Squamous Cell Carcinoma of the Upper Aerodigestive Tract

Abstract

Smoking-related tumors developing from exposed epithelium with squamous morphology share molecular pathways and genomic alterations. New paradigms are needed to characterize the shared set of tumors and ultimately propose therapeutic strategies. In the current proposal and ultimately through a proposed SPORE grant, we intend to break through historical boundaries of anatomy and disease classification to study squamous tumors of the upper aerodigestive system. ***Project #1: Mutational and Gene Expression Characteristics Associated with Radiation-Resistant Laryngeal Squamous Cell Carcinoma.*** This project seeks to deepen preliminary observations that genomic alterations may, in fact, play a major role in the therapeutic efficacy of radiation. Importantly, UNC brings a unique population-based sciences approach to this area through the use of the largest case-control study ever executed in this

area, run by project-PI Andy Olshan. ***Project #2: The role of NRF2 in squamous cell lung carcinoma.*** *NFE2L2* (aka NRF2) is among the most commonly mutated genes in all cancers and is the most commonly mutated oncogene in squamous cancers of any anatomic site. Recently, we generated a novel genetically-engineered mouse model (GEMM) harboring an activating mutation in NRF2. Although we are aware of one other NRF2 GEMM, ours is the first to model a human-derived activating mutation and the first to do so in the context of squamous cancer. To support our SPORE application, it is vital to characterize this newly developed animal model for its relevance to the etiology of squamous cancer as proposed in Specific Aim #1. The results from Specific Aim #1 will complement our proposed studies in Specific Aims #2 and #3 that examine the phenotypic impact of NRF2 activation in patient-derived primary cells and human tumors, respectively. ***Project #3: Targeting chondroitin sulfate proteoglycan 4 (CSPG4) using CAR T cells for head and neck cancer.*** Recent work in immunotherapy appears poised to push squamous cancer into the forefront of solid tumors in which immunotherapy offers high therapeutic potential. While the results of PD1-directed therapy are exciting, the fact that most patients progress is incentive for further therapeutic strategies in this disease. We propose innovative strategies to enhance the trafficking of these CAR-Ts to HNSCC tumor and to reduce local immunosuppressive mechanisms by combination of CAR-Ts with local tumor irradiation.

PI: Paul Dayton, PhD, Professor, UNC & NC State Joint Department of Biomedical Engineering

Project Title: Next-generation tools for quantitative imaging and analysis of cancer-associated angiogenesis in breast cancer

Abstract

Breast cancer is the most common cancer in the United States, with almost a quarter of a million cases expected in 2016. It is the second largest cause of cancer-related mortality overall, trailing only behind lung cancer, and the most common cancer in women. As early treatment of breast cancer has a high likelihood of success, early detection is crucial. Although x-ray mammography is a first-line screening tool in breast cancer, it suffers from numerous technical and physical limitations, including false positives, discomfort provided by breast compression and patient exposure to ionizing x-ray radiation. Mammography performs poorly in younger women, women with dense breasts, or women who have had breast augmentation. Additionally, vigilant screening is essential for post-mastectomy and radiation treatment patients, due to risk of recurrence near the chest wall. However, mammography is useless with chest wall imaging, and clinicians often instruct post-mastectomy patients with the 'watch and wait' discovery method of palpation. Breast ultrasound is a current clinical standard of care for those populations where mammography cannot be used. However, traditional ultrasound also has poor specificity and a high false positive rate. Furthermore, both mammography and standard ultrasound are challenged to detect small lesions (below a few millimeters in size), with the average detected lesion size around 1 cm. For more than three decades since Judah Folkman's seminal paper, angiogenesis has been well documented as a strong biomarker of malignancy. Nevertheless, there are currently no clinical imaging tools that can visualize the microvasculature fingerprint associated with tumor angiogenesis in patients. This has now changed, as PI Paul Dayton has recently developed 'acoustic angiography', a novel ultrasound

approach that enables visualization of tumor-associated angiogenesis and vascular abnormalities in lesions as small as 2-3 millimeters *in vivo*. Our overarching goal is to further expand our understanding and imaging capabilities of microvascular angiogenesis, and to further develop detection of angiogenesis as a biomarker into a new clinical diagnostic approach for early cancer detection and improved lesion differentiation. *Our fundamental hypothesis is that we will improve the sensitivity and specificity of small breast tumor detection using new ultrasound technologies designed to image tumor-associated angiogenesis, rather than the tumor mass itself.* In this Tier 3 UCRF project, our group of investigators will expand our research team and advance approaches to detecting angiogenesis as a biomarker of cancer using ultrasound. Over the two-year project period, we will prepare a P01 for NCI PAR-15-023 which will include basic science research, technology development, and preclinical and clinical studies. Our direction will involve four unique projects, uniting basic scientists, engineers, and clinicians from two universities (UNC Chapel Hill and NC State University), focused on improving detection and quantification of tumor-associated angiogenesis and understanding its signature in malignant and benign disease. We will also monitor progress on defining the new "National Cancer Moonshot Initiative" recently unveiled by Vice-President Joe Biden to determine if our ongoing work is a good fit for that funding mechanism as it evolves.